UNIVERSITY OF LIVERPOOL
Institute of Infection and Global Health

Development of climate-driven models for mosquito-borne disease risk in the UK

Thesis submitted in accordance with the requirements of the University of Liverpool for the degree of Doctor in Philosophy by Soeren Metelmann.

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I, Soeren Metelmann, confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.

Soeren Metelmann

Abstract

Mosquito-borne diseases are spreading around the globe and frequently emerge in new regions. An increasing globalisation, urbanisation and climate change all contribute to this spread. And this spread is even worrying for the temperate UK: there is strong concern that vectors and diseases could arrive with a warming climate. The Asian tiger mosquito *Aedes albopictus*, able to transmit more than 20 different viruses to humans, has recently become established over large parts of Europe. It has already caused disease outbreaks in Italy, France, Croatia and Spain and its eggs have now been found in the UK too. In this work we present the development of several climate-driven models to analyse the spread and dynamics of this vector species. A range of regional and global climate data sets has been used to assess the mosquito's ability to become established, to spread and to transmit diseases in the UK and elsewhere. The models are validated against various mosquito recordings, mosquito abundance data and disease incidence data sets. We find that for now, only some densely populated and high importation risk areas in south-east England seem to be suitable for long-term *Ae. albopictus* survival. Future scenarios suggest that the mosquito could become established over larger parts of the UK though, spreading over Southern England within 30 years once introduced. We also use a laboratory study to analyse if European *Ae. albopictus* show any adaptation to colder climates that would allow the species to expand its range in Europe even further. Though we do find some differences in larval development in comparison to tropical strains, the results are not quite clear. Finally, we model arbovirus transmission by *Ae. albopictus* in countries where the species is endemic and, in a second step, apply findings to the UK. Results indicate that the UK is not yet warm enough to enable mosquito populations to build up to high numbers and effectively transmit arboviruses. Individual cases of disease transmission in summer months cannot be excluded though. General findings demonstrate the importance of using detailed vector and infection ecology when modelling mosquito-borne diseases, especially for temperate regions.

Acknowledgement

First of all, I would like to thank my three supervisors: **Andy Morse**, I really appreciate how much time and interest you put into my PhD, **Matthew Baylis**, thanks for a lot of organisation and pushing me on, and **Jolyon Medlock**, thank you for encouraging conversations and suggestions. I would chose the same supervisor team if I had to do it all again. I thank my unofficial fourth supervisor, **Cyril Caminade**, for getting me started, interesting discussions and being a reliable lunch compagnon. Many thanks to a lot of staff and PhD students from different offices, the HPRU, geography and other departments: **Arturo, Ben, Jenny, Liz, Marcus, Maya, Merit, Rachael, Raquel, Sara** and **Steph** to name just a few. You have all made Liverpool Uni a great place to work at. I am grateful to **Qiyong Liu**, **Liang Lu** and **Xiaobo Liu** for their support during my placement in China. I also thank **Lina Cao** for her organising help, as well as the whole **ICDC team** at China CDC for making my stay in Beijing a fantastic experience. Thanks to **friends** and **family** for frequent visits from near and far and to **Mersey Rowing Club** and its members for generally keeping me sane. Last but not least, I am very grateful to my wife **Andrea** for her constant support and patience - you waited long enough for our honeymoon.

Author contribution

Apart from my supervisors, other people contributed to the presented works. Cyril Caminade helped in many ways, from introducing me to climate data handling, to providing data sets and maintaining IT infrastructure for the whole working group.

Parts of chapter 1 and the conclusion have been published as an opinion piece

Metelmann, S and Baylis, M (2017) 'What can climate-driven models teach us about the Zika outbreak?', Infectious Diseases Hub.
https://www.id-hub.com/2017/04/07/what-can-climate-driven-models-teach-us-about-the-zika-outbreak/

I wrote the opinion piece with inputs and comments from Matthew Baylis.

Parts of chapter 2 have been published as

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http://doi.org/10.1098/rsif.2018.0761

I designed the study together with Andy Morse and developed the model together with Andy Morse, Cyril Caminade and Matthew Baylis. I conducted the analysis and wrote the manuscript that was the basis for this chapter with inputs and comments from all co-authors.

The work presented in chapter 4 was co-supervised by Qiyong Liu from Jinan University/China CDC. Both Liang Lu and Xiabo Liu from China CDC provided mosquito data and gave advice concerning the mosquito ecology in China.

Parts of chapter 5 have been published as

Caminade, C, Turner, J, Metelmann, S, Hesson, JC, Blagrove, MSC, Solomon, T, Morse, AP and Baylis, M (2017), 'Global risk model for vector-borne transmission of Zika virus reveals the role of El Niño 2015.', PNAS, 17114(1), 119–124.
http://doi.org/10.1073/pnas.1614303114

In this project, I calculated global transmission risks in collaboration with the lead author Cyril Caminade. I was also involved in the model parametrisation and commented on the manuscript drafted by Cyril Caminade. Plots for the Zika outbreak shown in results and appendix of chapter 5 have been created by me before manuscript submission in 2016. The part of the arbovirus transmission study on Europe was undertaken independently by me.

A couple of people were involved in the laboratory experiment in chapter 6. Marcus Blagrove helped to organise mosquito eggs, Ken Sherlock assisted with setting up the experiment and Arturo Hernandez-Colina took over lots of monitoring shifts on weekends.

Given all these contributions, I decided to write this thesis in first person plural instead of singular.

Contents

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Abbreviations

AUC	Area under curve
BatV	Batai virus
BI	Breteau index
CalV	Calovo virus
CI	Container index
ChikV	Chikungunya virus
DDE	Delay differential equation
DTR	Diurnal temperature range
DenV	Dengue virus
ECDC	European Centre for Disease Control and Prevention
EEEV	Eastern equine encephalitis virus
EET	Elementary effects test
EIP	Extrinsic incubation period
IIP	Intrinsic incubation period
InkV	Inkoo virus
JEV	Japanese encephalitis virus
LCV	La Crosse virus
MBD	Mosquito-borne disease
OckV	Ockelbo virus
ODE	Ordinary differential equation
PDE	Partial differential equation
PHE	Public Health England
R_0	Basic reproduction number
RCP	Representative Concentration Pathway
RH	Relative humidity
RMSD	Root mean squared displacement
RMSE	Root mean square error
RMST	Restricted mean survival time
ROC	Receiver operating characteristic
RVFV	Rift Valley fever virus
SinV	Sindbis virus
SLEV	St Louis encephalitis virus
TahV	Tahyna virus
TSS	True skill score
UsuV	Usutu virus
WEEV	Western equine encephalitis virus
WHO	World Health Organization
WNV	West Nile virus
YFV	Yellow fever virus
ZikV	Zika virus

Chapter 1

Introduction

Mosquitoes are the most important biological disease vectors today. They transmit a whole range of viruses and parasites and can thus cause outbreaks of malaria, dengue, Zika and many other diseases. Control programmes reduced mosquito numbers and thus contained certain diseases with some success in previous decades. But at the same time, other mosquito-borne diseases were on the rise and emerged in new regions. This spread to new regions, requiring the previous introduction of vector species or the presence of competent endemic mosquitoes, is even worrying for the UK. Despite its temperate climate, there has been transmission of mosquito-borne diseases in the UK in the past and there is strong concern that new diseases could arrive with a warming climate. In this chapter, we give an overview about the British mosquitoes, those that might be introduced in the future and their abilities to transmit diseases to humans. We then explain how mathematical models can be developed to better understand the dynamics of mosquito populations and their role in disease transmission. We conclude by outlining the scope of this thesis.

1.1 Mosquitoes

Mosquitoes (Culicidae) are considered the most deadly animals in the world (Gates, 2014). Female mosquitoes bite human and other vertebrate hosts to consume their blood as they need the protein for egg production. During the act of biting, they can transmit a variety of deadly pathogens: Protozoans causing malaria, viruses causing dengue, chikungunya, Zika, yellow fever, and many more, as well as nematodes causing lymphatic filariasis. The family Culicidae constitutes of two subfamilies: Anophelinae with *Anopheles* mosquitoes present in the UK and Culicinae with five genera present in the UK.

1.1.1 British Mosquitoes

A total of 36 mosquito species have been recorded on the British Isles but not all of them are classified as endemic (Harbach et al., 2017). Some species are only a biting nuisance for humans, some could play a role in the transmission of diseases (Blagrove, 2016). Here, we give a brief overview over the most common genera.

Anopheles ssp.

Mosquitoes of the genus *Anopheles* are infamous for their transmission of malaria. There are six species present in the UK, all of which are potential malaria transmitters for either *Plasmodium vivax* or *P. falciparum* (Snow, 1998; Reiter, 2000). There is debate over which species was the main malaria vector in the UK in earlier years; *An. plumbeus* or *An. atroparvus* (Shute, 1954; Dobson, 1980). All species but *An. algeriensis* and *An. daciae* are widespread and frequently bite humans. Some are also domesticated, meaning that they prefer to rest in houses like *An. messeae* and *An. atroparvus* from the *An. maculipennis s.l.* complex (not to be confused with the species *An. maculipennis s.s.* itself, which is not present in the UK). Note that *An. daciae* from the same complex was only recently identified as new species with molecular methods (Nicolescu et al., 2004). Apart from malaria, mosquitoes of this genus could transmit the West Nile virus (WNV) (*An. plumbeus, An. messeae*) and the Batai virus *An. maculipennis s.l.* (Becker et al., 2010; Kampen et al., 2016).

Aedes ssp.

Aedes is the most represented genus in the UK with 14 species, including some of the world's most widespread pest mosquitoes (Reinert, 1973). The biggest group of *Aedes* mosquitoes belongs to the subgenus *Ochlerotatus*, which was classified as its own genus from 2000 until 2015, when it was reclassified as an *Aedes* subgenus (Reinert et al., 2004; Wilkerson et al., 2015).

Contrary to the other genera, most *Aedes* mosquitoes overwinter in the stage of desiccated eggs. Females start to lay eggs that go into a diapausing state in autumn, which can resist low temperatures during winter. This state is induced by low temperatures and shorter photoperiods (Vinogradova, 1975). In spring, egg hatching might be induced by higher temperatures and

longer days (Lacour et al., 2015).

Species of this genus are important disease vectors. Apart from the West Nile virus, *Aedes* mosquitoes in Britain are competent for viruses causing Sindbis (*Ae. communis, Ae. cinereus, Cx. torrentium*), Western, Eastern, and Venezuelan equine encephalitis (*Ae. vexans, Ae. dorsalis*), Rift Valley fever (*Ae. vexans*, but only in Africa), California encephalitis (*Ae. dorsalis*), and Tahyna (*Ae. vexans, Ae. detritus*) (Turell et al., 1982; Miller et al., 2002; Medlock et al., 2007; Jöst et al., 2010; Becker et al., 2010; Li et al., 2014). Even more importantly, invasive *Aedes* species that have become established in continental Europe and might be subsequently introduced to the UK are very competent disease vectors, see section 1.1.2.

Culex ssp.

Culex mosquitoes are very important disease vector species too. Some species bite multiple vertebrate hosts, thus facilitating zoonotic infections. Moreover, like *Aedes* species, they are able to transmit certain viruses maternally (Baqar et al., 1993; Nelms et al., 2013).

A very common species is *Cx. pipiens pipiens*. This species is competent for a range of different pathogens including viruses causing West Nile fever, St. Louis encephalitis, Sindbis, Tahyna, as well as the nematodes *Wuchereria bancrofti* and *Brugia malayi* causing filariosis (Harbach, 1988; Bartholomay et al., 2003; Fischer et al., 2008; Jöst et al., 2010). Moreover, this species is probably a main vector for the recently spreading Usutu virus in Europe (Nikolay, 2015).

Cx. pipiens molestus is listed as a biotype of *Cx. pipiens pipiens* while genetic analyses suggest that the two are actually distinct species, with *Cx. pipiens molestus* descending from *Cx. pipiens pipiens* and having adapted to warmer climates (Fonseca et al., 2004). While *Cx. pipiens pipiens* preferentially feeds on birds, *Cx. pipiens molestus* aggressively bites humans. Until recently, it was considered unlikely that these biotypes/species interbreed (Byrne and Nichols, 1999). But in 2014 Austrian scientists observed cross mating with the resulting hybrid mosquitoes feeding on both birds and humans, making them a potent bridge vector for e.g. the West Nile virus (Zittra et al., 2016; Vogels et al., 2016). Apart from the West Nile virus, *Cx. pipiens molestus* might be able to transmit chikungunya (Yamanishi et al., 1980).

Another species, *Cx. modestus*, has established in Kent in recent years and is spreading in the area (Golding et al., 2012; Vaux et al., 2015). This species is believed to be the main vector in WNV transmissions in France since 2000 (Balenghien et al., 2006). The locally occurring *Cx. europaeus* (previously known as *Cx. territans*) could be able to transmit WNV too (Medlock et al., 2005).

Culiseta ssp.

Culiseta mosquitoes are cold adapted and somewhat bigger than other mosquitoes. Seven species of *Culiseta* mosquitoes are present in the UK, some of which can transmit the West Nile virus (*Cs. annulata, Cs. morsitans* and *Cs. litorea*) (Medlock et al., 2005). Other diseases

include Sindbis (*Cs. morsitans*) and Tahyna (*Cs. annulata*)[1] (Francy et al., 1989; Danilova, 1972). Note that the adult *Cs. annulata* is easily confused with *Ae. albopictus* due to its white and grey pattern but is larger, 10 to 13 mm compared to 3 to 10 mm (Booy et al., 2015).

Others

There are two more species that do not belong in any of the former genera; *Orthopodomyia pulcripalpis* with a few occurrences and the more widespread *Coquillettidia richiardii*. Only *Cq. richiardii* readily bites humans and might be able to transmit WNV and Osmk haemorrhagic fever viruses, normally transmitted by ticks (Becker et al., 2010).

1.1.2 Mosquitoes that might establish in the UK

Six *Aedes* species have been introduced into mainland Europe since the 1990s, some of which are very competent disease vectors (Medlock et al., 2012). Before these species can reach the UK, they first have to cross the English Channel. But crossing such a strait can be very difficult for mosquitoes as can be seen from two species at the Strait of Gibraltar (*An. atroparvus* in Spain and *An. labranchiae* in Morocco) (Cranston et al., 1987). However, there is a frequent exchange of cars, lorries, trains and cargo between the continent and the UK through ferries and the Channel tunnel that facilitates introductions of non-endemic species. Whether an invasive mosquito can establish in the UK, once introduced, depends on place and time of the introduction event, competing species and their ability to cope with the British climate (Medlock et al., 2015). The current distribution and spread of the invasive mosquito species can be followed on ECDC Vectornet (2019).

Aedes albopictus

The Asian tiger mosquito *Ae. albopictus* is considered to be one of the most invasive species worldwide (IUCN, 2018). Originating in South East Asia, it has been introduced to Europe multiple times: in the 1970s into Albania (Adhami and Reiter, 1998), in 1990 into Italy (Sabatini et al., 1990) and in recent times into the Netherlands (by ship cargo and by plane) (Scholte et al., 2008; Ibañez-Justicia et al., 2017). Especially since its introduction into Italy, it has spread along the Mediterranean sea, see Figure 1.1. A reason for its invasive success are its drought resistant eggs that can be transported over long distances: The female mosquito is attracted by small pools of water, for example in used tyres or lucky bamboo pots that get shipped around the world. Having arrived at their new location, the larvae hatch when exposed to water (Vaux and Medlock, 2015). Moreover, the eggs can undergo a diapause to resist colder winter temperatures (Mori and Wada, 1978), allowing temperate regions to be colonised (Lacour et al., 2015).

It was already known from South East Asian strains that *Ae. albopictus* shows a high ecological plasticity concerning temperature and precipitation regimes (Paupy et al., 2009). In Europe, it thrives in a climate range with a mean winter and annual temperatures above 0 °C and 11 °C,

[1] even though not very efficiently transmitted

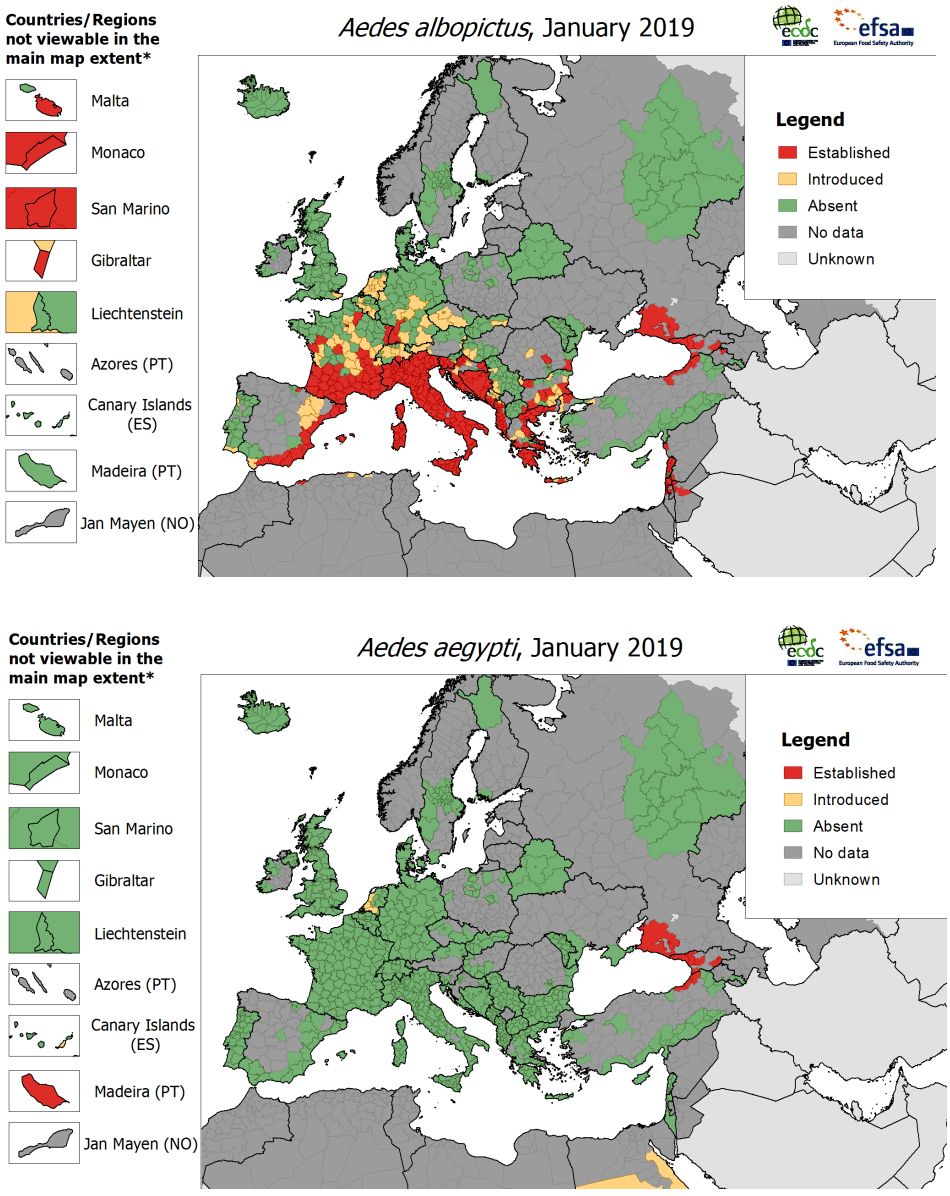

Figure 1.1: Vector distribution in Europe Current distributions of *Aedes albopictus* and *Ae. aegypti*. Taken and adapted from ECDC Vectornet (2019).

respectively, and annual rainfall above 500 mm (Kobayashi et al., 2002; ECDC, 2009; Roiz et al., 2010). However, populations have been found in regions with a mean annual temperature of 5 °C or annual rainfall of only 290 mm (Benedict et al., 2007), with heavy artificial irrigation creating breeding habitats in the latter case. Some populations have adapted well to human urban areas, while other populations can be found on uninhabited islands or areas (e.g. Tsuda et al., 2001; Lacroix et al., 2012). The female mosquito thus lays its eggs into a wide range of water containers, ranging from tree holes to man made plastic cups and flower vases (Delatte et al., 2013). It has also been shown by Dieng et al. (2010) that this mosquito can develop indoors, allowing for a climate independent development[2].

[2]Despite being somewhat domesticated, the name Aedes originates from the old Greek word *aēdēs* for un-

Ae. albopictus is a very effective disease vector. It can transmit more than 20 arboviruses and filarial worms affecting humans, pets and livestock, among which are for example the West Nile and yellow fever viruses and *Dirofilaria* worms (Paupy et al., 2009; Medlock et al., 2006; Genchi et al., 2009). It was also responsible for several dengue cases and chikungunya outbreaks in Italy and France in the last five years (Rezza et al., 2007; Schaffner and Mathis, 2014; Venturi et al., 2017). This mosquito is a very potent vector for zoonotic diseases because it feeds on mammals, birds, reptiles, and amphibians (Niebylski et al., 1994) but prefers to feed on humans in urban areas (Kamgang et al., 2012; Faraji et al., 2014).

Climate scenarios suggest that *Ae. albopictus* could establish in the southern UK if introduced (Caminade et al., 2012) and in September 2016, the first eggs have been found in Kent by a surveillance team of PHE (2017).

Ae. aegypti

Ae. aegypti is one of the most widespread mosquito species worldwide. As is the case for *Ae. albopictus*, its broad climate tolerance has made this vast spread possible (Campbell et al., 2015). Moreover, *Ae. aegypti* does not entirely rely on rainfall; it prefers artificial water containers for breeding (Jansen and Beebe, 2010).

Unlike *Ae. albopictus*, *Ae. aegypti* is not present in northern Europe. It is restricted by cold winter temperatures because it cannot produce winter diapausing stages (Weaver and Reisen, 2010). It was, however, previously established in the Mediterranean for at least two centuries until it vanished in the 1950s (Holstein, 1967). During this time, it was also introduced into the UK. In 1865, it successfully reproduced in Swansea during one summer and was even linked to the transmission of yellow fever. In that year, infected mosquitoes from a Cuban ship encountered exceptionally warm and suitable climate conditions in the UK. They quickly reproduced and transmitted the virus in the harbour city, resulting in 15 deaths (Surtees et al., 1971; Meers, 1986). Now, however, *Ae. aegypti* is only present in the eastern Black Sea region and on Madeira, where it was recently introduced (Seixas et al., 2019), see Figure 1.1. On Madeira, this species has a strong impact on human health: it was responsible for a dengue outbreak in 2012 (ECDC, 2012). In October of that year, the first local cases were reported and during the following seven months, this probably temperature-driven outbreak caused more than 2 000 cases and 81 exported cases to mainland Europe (Lourenço and Recker, 2014).

In addition to dengue, *Ae. aegypti* can transmit yellow fever (hence its common name; yellow fever mosquito), chikungunya, and Zika virus (Li et al., 2012). What makes this mosquito especially important for disease transmission is its strong preference for human hosts (Gould and Higgs, 2009; Saifur et al., 2012) as well as its feeding behaviour, biting multiple hosts during one gonotrophic cycle (Weaver and Reisen, 2010).

pleasant and not from the Latin word *aedes* for house.

However, its incapability of overwintering in cold climates suggest that *Ae. aegypti* is not able to establish in the UK (Scholte et al., 2010), even though it could well be introduced and reproduce in the summer months (Surtees et al., 1971).

Others

Ae. japonicus is, like *Ae. albopictus*, one of the top invasive species worldwide (IUCN, 2018). It is adapted to northern European temperatures, laying diapausing eggs for winter, and can develop in water temperatures as low as 10 °C (Scott and Morrison, 2003). It has been introduced to France in 2000, and Belgium in 2002, probably through used tyres (Versteirt et al., 2009; Kaufman and Fonseca, 2014). Since then, it has spread in central Europe (Ibáñez-Justicia et al., 2014; ECDC Vectornet, 2019). Even though *Ae. japonicus* feeds on mammals including humans, it is not known as a disease vector (Medlock et al., 2015). However, it has been shown to be competent for WNV, CHIKV, DENV, ZIKV, and La Crosse (Schaffner et al., 2011; Harris et al., 2015; Jansen et al., 2018). This species might also be an ecological problem, as it might out-compete local species like *Cx. pipiens* (Kampen and Werner, 2014), thus changing ecosystems.[3]

Ae. atropalpus has been introduced to Europe multiple times but could always be eradicated (Romi et al., 1997; Scholte et al., 2009). It is believed to be able to survive in northern Europe (Medlock et al., 2015). While this species is autogenous, meaning that it does not have to take blood meals for the first egg development (O'Meara and Krasnick, 1970), it feeds on mammals including humans for subsequent egg development (Turell et al., 2001). Like *Ae. japonicus*, it is not linked to disease outbreaks yet but was shown to be competent for WNV and various encephalitis viruses (Turell et al., 2001; Scholte et al., 2009).

There are three remaining species: *Ae. koreicus* has established in small areas in Belgium, Germany and Italy (Capelli et al., 2011; Boukraa et al., 2015) and might be competent for JEV (Miles, 1964), chikungunya (Ciocchetta et al., 2018) and the nematode *Brugia malayi* (Cho et al., 2012).
Ae. triseriatus has been introduced with used tyres to France in 2004 but has been eradicated (Medlock et al., 2012; ECDC Vectornet, 2019). It is a vector for the La Crosse virus and potentially for other arboviruses (Reese et al., 2009).
Culex pipiens quinquefasciatus, a competent vector for many diseases, only has a single report in Greece (Walter Reed Biosystematics Unit, 2012). The species could become established in larger parts of Europe though (Samy et al., 2016).

1.1.3 Summary

As the repeated re-classification of *Ochlerotatus/Aedes* mosquitoes shows, it is not easy to achieve a stable classification that reflects evolutionary relationships, see Figure 1.2. Mosquito groups are not necessarily monophyletic, which has as a result that for example in the genus *Aedes* some *Ochlerotatus* species can be more closely related to *Stegomyia* species than among

[3]Though there is a debate if mosquitoes significantly contribute to ecosystems at all (Fang, 2010).

each other. Only for Anophelinae mosquitoes, there is strong morphological and molecular evidence to be monophyletic. For the remaining groups, there is simply too little genomic and phylogenetic data available, see (Reinert et al., 2004, 2006; Harbach, 2007; Shepard et al., 2009; Reidenbach et al., 2009; Wilkerson et al., 2015) for further reading.

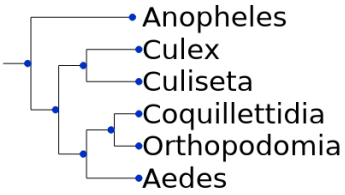

Figure 1.2: Mosquito phylogeny Most probable relationship among Culicidae mosquitoes. (Adapted from Reidenbach et al. (2009)).

Table 1.1 gives an overview over all British mosquitoes and those that might be introduced, their abundance, feeding and overwintering behaviour, as well as their vector competence. For detailed distributions of species compare for example Snow (1998); Danabalan et al. (2014); ECDC Vectornet (2019).

Of all species present in the UK, only a couple are simultaneously widespread, biting humans, and able to transmit pathogens, compare Table 1.1. Species of interest are *Ae. cinereus*, *Cq. richiardii*, and *Cx. modestus* for West Nile virus transmission, and potential hybrids of *Cx. pipiens pipiens* and *Cx. pipiens molestus*, possibly combining human biting behaviour with vector competence. The risk of endemic mosquito species being disease vectors could be underestimated though, as most of them are not analysed for vector competence.

An even bigger threat to public health might be invasive mosquito species. All species that have been introduced to Europe in recent years are competent disease vectors and are thus also of interest for the UK. PHE is continuously monitoring seaports, airports and tyre companies to check for introductions of non-native species (Medlock et al., 2015; Vaux and Medlock, 2015; Medlock et al., 2017).

Table 1.1: UK mosquitoes and their diseases The different symbol sizes denote UK abundance: ●: widespread, •: regional/few, *: introduced, ○: absent. Host preference: ●: preferred, •: occasionally. Disease competence: ●: transmission to human observed, •: tested positive in any way. Overwintering stage: E: Eggs, L: Larvae, P: Pupae, A: Adult.

Scientific Name	UK	Humans	Mammals	Birds	Malaria	Dengue	Zika	West Nile	Usutu	Chikungunya	Sindbis	Tahyna	Inkoo	Batai/Calovo	other viruses	Nematodes	Winter
Anopheles																	
An. algeriensis	•	•	●		●												L
An. atroparvus	●	●	●		●			●						•		•	A
An. claviger	●	●	●		●									•		•	L
An. daciae	•	●	●	●	•									•			?
An. messeae	•	•	●	●	●			•						•	●		A
An. plumbeus	●	●	●	•	●			•								•	(E)/L
Aedes																	
(Aedes)																	
Ae. cinereus	●	●	●	●				●			●	•				•	E
Ae. geminus	●																E
(Aedimorphus)																	
Ae. vexans	•	●	●					●	•			●		•	●	•	E
(Finlaya)																	
Ae. atropalpus	○	●	●	●				•							•		E?
Ae. geniculatus	●	●								•						•	E/L
Ae. koreicus	○	●	●							•					•	•	E
(Hulecoeteomyia)																	
Ae. japonicus	○	●	●			•	•	●		•					●		E/(L)
(Ochlerotatus)																	
Ae. annulipes	●	●	●								•						E
Ae. cantans	●	•	●	●				●			•						E
Ae. caspius	●	●	●					●	•		•					•	E
Ae. cummunis	•	●									•	●	•				E?
Ae. detritus	●	●	●	•			•	•							•	•	L
Ae. dorsalis	•		●					•			•				●		E
Ae. flavescens	•	•	●	•							•						E
Ae. leucomelas	•	●															E?
Ae. punctor	●	•	●	•				•			•	●	•			•	E/L
Ae. rusticus	●	●															L
Ae. sticticus	•	●	●								•	•				•	E?
Ae. triseriatus	○	●	●	●	•			•							•		E
(Stegomyia)																	
Ae. aegypti	○	●	●			●	●	•		●					●	●	○
Ae. albopictus	*	●	●	●		●	●	•	•	●	●				●	●	E
Coquillettidia																	
Cq. richiardii	●	●	●	●				●				•		•			L
Culex																	
Cx. europaeus/territans	●	•	•	●				●									A
Cx. modestus	●	●	●	●				●				●			•		A
Cx. p. pipiens	●	•	•	●				●	•		•	•				•	A
Cx. p. molestus	•	●		•				●		•						•	E/L/A
Cx. p. quinquefasciatus	○	●	•	●			•	●		•					●	●	○?
Cx. torrentium	●			●							●						A
Culiseta																	
Cs. alaskaensis	•	●															A
Cs. annulata	●	●		●				•	•		•	•					E/L/A
Cs. fumipennis	●			•													?
Cs. litorea	●	•		●				•									L
Cs. longiareolata	•	•		●													L
Cs. morsitans	●	•		●				•			•				•		L
Cs. subochrea	•	●	●														(L)/A
Orthopodomyia																	
Or. pulcripalpis	•	•		●													L
Scientific Name	**UK**	**Humans**	**Mammals**	**Birds**	**Malaria**	**Dengue**	**Zika**	**West Nile**	**Usutu**	**Chikungunya**	**Sindbis**	**Tahyna**	**Inkoo**	**Batai/Calovo**	**other viruses**	**Nematodes**	**Winter**

References: Yamanishi et al. (1980); Cranston et al. (1987); Jetten and Takken (1994); Bartholomay et al. (2003); Medlock et al. (2005, 2007); Ponçon et al. (2007); Weissenböck et al. (2008); Hubálek (2008); Scholte et al. (2009); Medlock and Vaux (2009); Danabalan (2010); Becker et al. (2010); Li et al. (2014); Blagrove (2016); Kampen et al. (2016); PHE (2017); Ciocchetta et al. (2018); Jansen et al. (2018); ECDC Vectornet (2019); Prudhomme et al. (2019), Blagrove *et al.* (unpublished).

1.2 Mosquito-Borne Diseases

Mosquitoes can spread a variety of pathogens: protozoans, nematodes and viruses.[4] Female mosquitoes bite humans and other vertebrate hosts to consume their blood. If the host is infected with a pathogen, the mosquito can take it up and, depending on the mosquito's digestive tract, the pathogen either gets digested or it might also infect the mosquito. When the mosquito gets infected, the pathogen needs a certain amount of time (the extrinsic incubation period, EIP) to spread to the mosquito's extremities, replicate and build up numbers in its salivary glands (Mueller et al., 2010). Only then can the mosquito transmit the pathogen to the next host by biting. However, some viruses are also transmitted mechanically, adhering to the mosquito's proboscis like the Myxoma virus (Cranston et al., 1987).

This section should give an overview of diseases that can be transmitted by British mosquitoes or those that might come the the UK.

1.2.1 Malaria

Malaria is commonly known as a tropical disease with the main malaria agent being the protozoan parasite *Plasmodium falciparum*. People infected with *P. falciparum* develop periodically occurring fever, chills, and spasms that can result in death especially among younger children. However, there are other malaria parasites that also have been present in Europe in previous centuries, including all four countries of the UK (Kuhn et al., 2003). Tertian malaria, commonly known as ague at that time, was caused by *P. vivax* and estimates go that in 1887 there were 112 000 cases in England and Wales which had a combined population of 30 million people at that date (Cranston et al., 1987). This would be a prevalence rate of 0.4%, comparable to e.g. South Africa today (WHO, 2018).

All types of human malaria parasites are transmitted by *Anopheles* mosquitoes. This link was established in 1897 by Ronald Ross who later received the Nobel prize for his discovery (Dobson, 1999). The first maps linking malaria to its vector were created at the beginning of the 20th century (Nuttall et al., 1901; Lang, 1918). In the following years, cases in the UK decreased due to wetland drainage and the local separation of livestock and humans (and hence mosquitoes and humans) (Dobson, 1980). The two world wars brought higher numbers of infected soldiers back into the country, while local cases remained low (12 after WWII) (Cranston et al., 1987). The last record of locally acquired tertian malaria in Britain dates back to these times, and it was eradicated from Europe entirely in the 1950s (Chin, 2004; Vaux and Medlock, 2015). For the next decades, only travel related cases and so called airport mosquitoes remained an issue (Whitfield et al., 1984). Two *P. falciparum* malaria cases were for example reported in Germany in 1997, transmitted by local *An. plumbeus* mosquitoes (Krüger et al., 2001). However, after being absent from Europe for over 50 years, malaria cases caused by *P. vivax* have re-emerged

[4] It is remarkable that mosquito-borne diseases comprise the groups of viruses, protozoans, and eumetazoans but not the large groups of bacteria or archaea. There are bacterial vector-borne diseases though, infamous examples would be plague, caused by the bacterium *Yersinia pestis* and transmitted by fleas and Lyme disease, caused by *Borrelia* bacteria and transmitted by ticks.

in Greece (HCDCP, 2016).

Concerning the UK, it is unlikely that malaria will return to become a big issue again for two reasons: 1) there are a number of effective antimalarial drugs available to the public health system to treat the infection, and 2) malaria is not zoonotic, meaning that it does not have an animal reservoir and hence would have to be maintained in the human population.

1.2.2 Arboviruses

The group of **ar**thropod-**bo**rne viruses is very diverse, with viruses endemic to Europe belonging mostly to the three groups of Flaviviridae, Togaviridae, and Bunyavirales (formerly Bunyaviridae). In order to see if any two viruses are likely to have some characteristics in common, for example the sharing of a vector, it is useful to look at their relationship. Unfortunately, unlike for example mosquitoes, viruses have many evolutionary origins and cannot be included in a single phylogenetic tree. It is, however, possible to build phylogenetic trees for the individual virus families, see Figure 1.3.

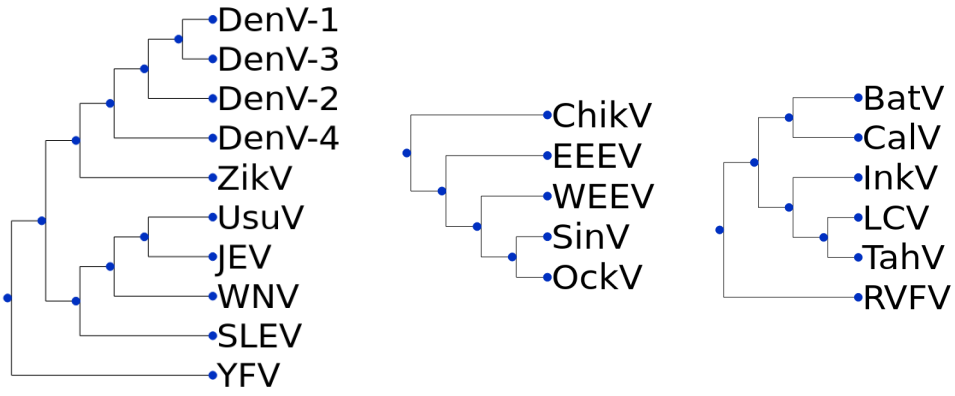

Figure 1.3: From left to right: Flaviviridae, Togaviridae, and Bunyavirales. Flaviviridae and Togaviridae are (+)ssRNA viruses while Bunyavirales are (-)ssRNA viruses. All mosquito-borne Togaviridae fall into the genus Alphavirus. Note that these unrooted trees only reveal relationships and branch length does not denote evolutionary time. Adapted from Nunes et al. (2005); Bolling et al. (2015); Shchetinin et al. (2015).

Dengue

Dengue is a viral infection that has spread worldwide, with estimates between 50 million (WHO, 2009), 380 million (Bhatt et al., 2013) and even 3.8 billion (Brady et al., 2012) people affected by this disease. There are four different serotypes (DenV-1, -2, -3, -4) with possibly a fifth serotype discovered recently (Normile, 2013). Most cases are asymptomatic but 20% of infections show flu-like symptoms, including fever and rash. In rare occasions, especially when there was a prior infection with another serotype, it can lead to severe haemorrhagic fever or dengue shock syndrome, which can have a fatal outcome (WHO, 2009).

Dengue is endemic to the tropics but has rapidly spread to other countries in the second half

of the 20^{th} century (WHO, 2009), probably due to international travel, urbanisation (Gubler, 2004) and the spread of its main vector *Ae. aegypti*. Besides outbreaks in tropical regions (Dar et al., 1999; Koh et al., 2008; Wang et al., 2015), there had been one major outbreak in Europe on the Portuguese island Madeira in 2012 with 2 000 infections (Lourenço and Recker, 2014), as well as local cases in France, Croatia and Spain throughout the last ten years (LaRuche et al., 2010; Gjenero-Margan et al., 2011; Succo et al., 2016; ECDC, 2018*d*). The outbreak on Madeira could be linked to *Ae. aegypti*, while cases in continental Europe were linked to *Ae. albopictus*. Possibly due to its strong connection to the Commonwealth countries, the UK faces a couple of hundred travel related dengue cases each year (Vaux and Medlock, 2015). But no mosquito species in the UK has been linked to dengue transmission so far, compare Table 1.1.

Dengue viruses (DENV) can be transmitted maternally from female to egg (Rosen, 1987) but the importance of this mechanism in disease transmission is not yet clear (Grunnill and Boots, 2015). Such a vertical transmission to diapausing eggs would be necessary for dengue to become endemic in temperate regions like the UK as there is no virus reservoir in females in the winter, nor in humans who usually recover after a couple of days.

There are multiple approaches to fight dengue, for example the use of insecticides or the destruction of breeding habitats for the vector species. Another famous project is "Eliminate Dengue" in which mosquitoes get infected with the symbiotic bacterium *Wolbachia* and are subsequently released. The mosquitoes naturally spread the bacterium in the population and *Wolbachia* infected mosquitoes usually take up viruses with a lower rate and die earlier, thus reducing the spread of dengue (Moreira et al., 2009), see the project website `www.eliminatedengue.com`. Yet another approach that directly targets the virus are dengue vaccines. In 2016, a vaccine that was supposed to be effective for all four serotypes became available in Indonesia and the Philippines and was recommended by the WHO (WHO, 2016*a*). However, a vaccination campaign was stopped after the occurrence of incidences in children without pre-infections.

Zika

Zika is an emerging human infection that was first discovered in Uganda in 1947 but soon spread to other regions and continents (de Paula Freitas et al., 2016; Kindhauser et al., 2016). Recent years have seen Zika outbreaks in Micronesia in 2007 and in Oceania in 2013 (Duffy et al., 2009; Jouannic et al., 2016). But the largest outbreak occurred in 2015/16 in South America with several hundreds of thousands of infections, from Argentina in the south to Florida, US in the north (Hayes, 2009; Musso et al., 2015; WHO, 2016*c*; PAHO/WHO, 2017). Reasons for this massive outbreak were a completely susceptible population, the presence of two main vector species *Ae. aegypti* and *Ae. albopictus*, as well as the tropical climate (Ai et al., 2016).

Infections with the Zika virus (ZIKV) are similar to dengue, only 20% of infected people show symptoms and these are flu-like fever and rash. However, Zika infections are also linked to the development of Guillain-Barré syndrome, an auto-immune disease (Parra et al., 2016). Moreover, infection of women during pregnancy can lead to microcephaly in the child (Mlakar et al.,

2016). This led the World Health Organisation to announce a Public Health Emergency of International Concern in February 2016 (WHO, 2016*b*).

There have not been any confirmed cases of mosquito-transmitted Zika in the UK or continental Europe but 314 cases have been imported to date and the virus has probably been sexually transmitted once in the UK (PHE, 2019). With local competent vector species *Ae. detritus* or the newly introduced *Ae. albopictus*, and active virus replication above 18 °C, there is a chance for local Zika transmission in the UK (Blagrove *et al.*, unpublished).

West Nile

West Nile fever is caused by the West Nile virus that is transmitted mainly by mosquitoes and in a few cases by ticks (Lawrie et al., 2004). Birds are the main host for the West Nile virus, with humans only being a secondary host. Human infections go unnoticed in 80% of all cases, otherwise they show symptoms of a light flu. In very rare cases (0.6%) an infection can lead to an encephalitis or meningitis that can be fatal (Mostashari et al., 2001; Zou et al., 2010). In most endemic regions, it is considered a childhood disease as adults have acquired immunity.

The West Nile virus (WNV) is the most widespread encephalitic flavivirus globally (May et al., 2011). During the last 50 years, Europe experienced several outbreaks especially in the eastern parts (Hubálek and Halouzka, 1999) and in 2010 a larger outbreak occurred in Mediterranean Europe (Sambri et al., 2013). Since then, West Nile cases have re-emerged every year (Paz, 2015) with about 250 cases annually (ECDC, 2018*e*). Especially 2018 saw a large increase in numbers with about 2 100 cases reported in Europe (ECDC, 2018*e*). In the USA, West Nile was introduced in 1999 and has rapidly spread, causing several thousand cases annually (Petersen et al., 2012).

WNV does not have to be maintained in the human population as it has several avian and mammalian hosts (McLean et al., 2001; Dauphin et al., 2004). This makes it very hard to control the disease, especially with its high rate of asymptomatic cases. Moreover, the virus could be easily introduced into the UK by migrating birds. In fact, one working group found overseas and farm birds in southern England and Wales positive for West Nile virus antibodies (Buckley et al., 2003). There is, however, debate about the possibility of laboratory contamination resulting in positive findings in this study (Matthew Baylis, personal communication).

The West Nile virus is transmitted by mosquito species that are endemic to the UK, with the most important ones being *Cx. pipiens pipiens*, *Cx. pipiens molestus* and *Cq. richiardii*. The species *Cx. modestus* which has recently become established in Kent (Medlock et al., 2012), has probably played a major role in outbreaks in Romania in 1996 and France from 2000 to 2004 (Tsai et al., 1998; Balenghien et al., 2008). It is also transmitted by invasive species like *Ae. albopictus* (Vogels et al., 2017).

Chikungunya

Originally endemic in Africa and Asia, the chikungunya virus (CHIKV) has now spread to Oceania, Europe, and recently to the Americas together with its vectors *Ae. aegypti* and *Ae. albopictus* (Nunes et al., 2015). There are five regional virus variants that are genetically different (Parola et al., 2006). Unlike the other arboviruses discussed, *Ae. albopictus* is a better vector for a certain strain of the chikungunya virus than *Ae. aegypti* due to a single point mutation in the virus (Tsetsarkin et al., 2007; Vazeille et al., 2007). One study also found *Cx. pipiens molestus* to be competent for chikungunya (Yamanishi et al., 1980).

Chikungunya symptoms last for usually three days and include fever, muscle and joint pain, rash, and fatigue. In rare cases it can lead to long lasting joint pains or an encephalitis (da Cunha and Trinta, 2017). Asymptomatic courses are also possible (Chhabra et al., 2008). Host reservoirs include primates and rodents, but also rare cases of transmission from human to human by used needles or organ transplant (Thiberville et al., 2013), and also from mother to child during pregnancy have been observed (Robillard et al., 2006).

About three million people get infected annually, with a number of bigger outbreaks in recent decades (Thiberville et al., 2013). An epidemic in the DR Congo in 1999 caused 50 000 infections (Muyembe-Tamfun et al., 2003). In 2006, CHIKV was introduced into La Réunion, whose inhabitants had not acquired any prior immunity. One third of the population (260,000 people) got infected and about 250 people died (IVS, 2006; Josseran et al., 2006). The biggest outbreak so far occurred in India in 2006/2007 with an estimated 1.3 million people infected (Arankalle et al., 2007).

The disease has also reached Europe. It is believed that in 2007 a single infectious person travelled from India to Italy and caused a small outbreak with 300 infections near Ravenna (Angelini et al., 2007; Rezza et al., 2007). In 2017, there was another outbreak in Italy with about 500 people infected (Venturi et al., 2017). Local transmission in Italy was linked to *Ae. albopictus*, as were individual cases in southern France in 2010 and 2014 (Grandadam et al., 2011; Delisle et al., 2015). Apart from that, Europe and the UK face mostly travel related chikungunya cases (24 in 2013 and 300 in 2014 in the UK) (Vaux and Medlock, 2015; ECDC, 2018*a*).

Sindbis

The Sindbis virus (SINV) cause dengue-like symptoms such as an inflammation of joints or a rash (Laine et al., 2004). It can also cause long-lasting joint problems (polyarthritis) (Lwande et al., 2015). It is closely linked to the less pathogenic Ockelbo virus, causing Ockelbo disease in Sweden, as well as to viruses causing Karelian fever and Pogosta disease in Russia and Finland (Espmark and Niklasson, 1984; Shirako et al., 1991; Kurkela et al., 2004).

Humans are only secondary hosts with the main hosts being birds (Buckley et al., 2003). Sindbis

infections in humans usually occur in the summer and end in autumn (Kurkela et al., 2008). Vectors present in the UK include *Cx. torrentium*, *Cx. pipiens pipiens*, *Cs. morsitans*, *Ae. cinereus*, *Ae. cantans*, *Ae. annulipes*, and *An. maculipennis s.l.* (Francy et al., 1989; Medlock et al., 2007; Jöst et al., 2010). It is not known whether the virus overwinters in northern Europe in mosquitoes, birds or is re-introduced each year by migrating birds. In the UK, the virus has been found in birds (Buckley et al., 2003) but not in humans (Adouchief et al., 2016).

Tahyna

The Tahyna virus (TAHV) is widespread in Europe and antibodies have been found in rodents in the UK (Hubalek et al., 2004; Hubálek, 2008). An infection results in mild flu-like symptoms with one or two days of fever, in rare cases an encephalitis is possible (Bennett et al., 2011). It can be transmitted by a range of endemic species: *Ae. vexans, Ae. cantans, Ae. sticticus, Ae. caspius, Cx. pipiens pipiens*, and *Cs. annulata* (Medlock et al., 2007). For *Ae. vexans*, it was shown that the Tahyna virus can be transmitted to diapausing eggs and therefore overwinter in cold regions (Danilova and Ryba, 1979). Other host reservoirs seem to be primarily rodents and other mammals (Bárdoš, 1975; Hubálek, 2008).

Usutu

Usutu virus (USUV) is another emerging zoonotic disease that was first identified in Europe in 2001 in Austrian birds, but was soon discovered in other countries (Ashraf et al., 2015). Birds in southern England and Wales have been tested positive for Usutu virus antibodies, indicating that it is present in the UK too (Buckley et al., 2003), even though the climatic conditions might not be very suitable (Cheng et al., 2018). Infections with Usutu virus in humans only show severe neurological symptoms in very rare cases, while a retrospective study showed that symptomatic infections might have been more common (Gaibani and Rossini, 2017). While *Cx. pipiens* seems to be a main vector for this virus, other species have been also tested positive: *An. maculipennis s.l.* and *Ae. caspius* (Nikolay, 2015).

Others

The Batai or Calovo virus is widespread in Europe but does not seem to be of medical importance as no clinical disease has been reported so far (Gatz, 2006). If at all, infections only cause light symptoms in humans like headache or fever. Usual hosts for the Batai virus are bovids, pigs and deer, possibly birds too (Zhang et al., 2017). It is transmitted by species of the *An. maculipennis* complex, but isolates have been found in other species too, compare Table 1.1 (Francy et al., 1989; Becker et al., 2010). It is assumed that the virus overwinters in hibernating mosquito females (Becker et al., 2010).

Inkoo virus is present mostly in northern Europe but is unlikely to be of medical importance for the UK due to the absence of main avian hosts (Medlock et al., 2007). Present vectors include *Ae. caspius*, *Ae. communis* and *Ae. punctor* (Francy et al., 1989; Lwande et al., 2017).

1.2.3 Nematodes

Some nematodes can cause filariasis, a disease affecting skin, serous cavities or lymph (Melrose, 2002), leading to elephantiasis in rare cases. These nematodes are called filarial worms. The two species responsible for nearly all of the 120 million lymphatic infections in 83 countries are *Wuchereria bancrofti* (90%, tropical regions in Africa, South and Central America, and Asia) and *Brugia malayi* (10%, mostly SE Asia) (Taylor et al., 2010). Both *W. bancrofti* and *B. malayi* are transmitted by a range of species from the genera *Anopheles, Aedes* and *Culex* (Melrose, 2002; Cano et al., 2014). Most known vectors are not (yet) present in the UK, compare Table 1.1, only the endemic *Cx. pipiens pipiens* might be able to transmit filarial worms to humans (Bartholomay et al., 2003). But mathematical and meta analyses suggest that temperatures are not yet suitable for transmission of these nematodes in Northern Europe (Lardeux and Cheffort, 2001; Cano et al., 2014). Moreover, there are several treatments available (Taylor et al., 2005, 2010) so that these filarial worms are not going to be of great clinical importance in the UK.

There are, however, the heartworms *Dirofilaria immitis* and *D. repens*, common in southern Europe and frequently introduced into the UK (Masetti et al., 2008; Genchi et al., 2009; Agapito et al., 2018). Their primary hosts are dogs, but they can also infect other mammals, reptiles, and in rare cases humans (Muro et al., 1999). Vectors of *Dirofilaria* include a range of local *Aedes* and *Anopheles* species, as well as *Cx. pipiens molestus* (Medlock et al., 2007).

1.2.4 Summary

Mosquito-borne diseases, MBD, especially malaria, have been a problem for the UK for a long time but vanished with mosquito habitat degradation and better health care 50 years ago. The last five decades have seen almost no local transmission of MBD. Positive tests of bird's blood serums, however, indicate that West Nile, Usutu, Sindbis and Tahyna viruses could circulate in the UK (Buckley et al., 2003; Gould et al., 2006). Other viruses, such as dengue or chikungunya, are frequently imported with travelling cases in the range of dozens to a few hundred cases per year (ECDC, 2018*a*,*b*) but numbers could be much higher as most arboviruses infections are asymptomatic and would not be registered. That means that local transmission in the UK might have gone undetected, either because a course of disease was asymptomatic or simply because it was not identified as being caused by an arbovirus (Gould et al., 2006).

It should be noted that this is only the human health side though. Some of these pathogens and others not mentioned also affect animals, e.g. horses (Chapman et al., 2016), dogs (Agapito et al., 2018) or poultry and chicken (Brugman et al., 2018).

1.3 Climate-Driven Mosquito Modelling

Like all insects, mosquitoes are highly sensitive to climatic factors. Temperature and humidity affect mosquito development rates, longevity and biting behaviour (Alto and Juliano, 2001). Precipitation has both an indirect effect by influencing humidity and a direct effect on the availability and quality of breeding sites (Fontanarrosa et al., 2000). Other factors such as wind speed might also have an impact on daily mosquito activity (Service, 1980) and dispersal. Climate does not, however, only influence the mosquito. The transmission of viruses and other pathogens is highly sensitive to environmental temperatures too: the pathogens are replicating faster in the mosquito when it is warmer (Tjaden et al., 2013) and the mosquito's biting rate and its longevity are influenced by temperatures (Scott et al., 2000). Temperature thus has a big impact on the mosquito's vectorial capacity (Liu-Helmersson et al., 2016).

Given these climate sensitivities, it is not surprising that outbreaks of mosquito-borne diseases often follow extreme weather events. West Nile and dengue fever cases have been reported to increase after heat waves (Paz, 2006; Panhuis et al., 2015), Rift Valley fever and malaria outbreaks have followed flooding events (Epstein, 1999; Anyamba et al., 2001), and chikungunya and West Nile fever outbreaks have followed droughts due to increased water storage (Chretien et al., 2007; Wang et al., 2010).

Mathematical models are used to analyse the cause and course of these outbreaks and their links to climate factors to better understand where and when the next outbreak might occur. Mathematical models can to be divided into two big categories: Dynamical and statistical models. Statistical modelling is used to analyse relationships between variables with the help of probability theory. Examples are relationships between environmental factors and local or global mosquito distributions (Roiz et al., 2011; Kraemer et al., 2015) or between climate factors and disease incidence (Paz, 2006; Wang et al., 2010; Burtis et al., 2016). While statistical models can detect correlations, they do not explain any underlying causalities. This can lead to inadequate predictions, for example if non-linear processes are involved (Kendall et al., 1999).

In that case, dynamical models might be better suited. These models describe the interactions and change rates of climate factors and other variables which require a deeper understanding of the underlying processes. Climate-driven dynamical models have been used to describe the effects of vector control on *Anopheles* mosquitoes (White et al., 2011) or the transmission dynamics of dengue (Chen et al., 2012). Some studies apply both dynamical and statistical models to the same problem, often with varying results, see for example Cheng et al. (2018) for the risk of Usutu transmission in Europe.

The start in dynamical mosquito-borne disease modelling was made by Ross (Ross, 1911), investigating the epidemiology of malaria. Four decades later, Macdonald developed these early models further (Macdonald, 1950) leading to the famous Ross-Macdonald theory (Smith et al., 2012). Still today, most models for mosquito-borne diseases resemble the Ross-Macdonald model approach in many aspects (Reiner et al., 2013). Others researchers such as Kermack and

McKendrick built upon the models by Ross, leading to the susceptible-infected-recovered (SIR) models around 1930 (Kermack and McKendrick, 1927, 1932, 1933). While those early works focussed just on the transmission risk, the following models went more into detail and looked at certain parts of the transmission cycle. Shapiro et al. (2017) and the Liverpool Malaria Model (Hoshen and Morse, 2004; Ermert et al., 2011) simulate each component of malaria transmission in detail, Dye (1984) focuses solely on population dynamics of the vector species *Ae. aegypti* and other models look for example at virus-antibody interactions in the host cells (Ben-Shachar and Koelle, 2015; Clapham et al., 2016).

As mosquito-borne diseases have always been a burden of the tropics, most modelling work focussed on these regions historically. But the appearance of invasive mosquitoes together with disease outbreaks in the temperate zones have attracted the attention of modellers too. A lot of studies have been published recently, investigating the climatic and environmental suitability of disease transmission in Europe for pathogens such as Usutu (Cheng et al., 2018), Zika (Rocklöv et al., 2016) or West Nile (Vogels et al., 2017). A few vector models focus on the UK specifically, such as a simpler climate envelope model for *Ae. albopictus* by Medlock et al. (2006) or a dynamic model for *Cx. pipiens* (Ewing et al., 2019).

1.3.1 Modelling Process

A mathematical model is the representation of a part of the real world. Its main purpose is the reduction of the real world's complexity such that the user can better understand and make predictions about the considered process. A first step in mathematical modelling is to classify variables and factors into those that should be included in the model and those that can be neglected as they would have too little or no impact on the model results. The model is thus only an approximation of the real world process, but it can be a useful one (Box and Draper, 1987).

The approximation of a real world process by variables with relationships and parameters yields a first representation: the real world model, see Figure 1.4. This can be used to understand and visualise the process and make some first qualitative predictions. To make quantitative predictions, this real world model has to be translated into mathematical equation which requires further assumption: Whether it is appropriate to model the dynamics continuously or in discrete time steps or whether a deterministic or stochastic approach should be used have a great influence on the mathematical model design.

When the mathematical equations are set up, they can either be solved analytically or, if they are too complex, have to be translated further into a computer model to be solved numerically. Again, the translation of the mathematical equations into computer code requires choices between precision and computation time and between various solving methods that control numerical errors and uncertainties (Oberkampf et al., 2002). In most cases, a mix between analytical and numerical methods is applied to a problem, using for example analytical results of steady states to yield insights of model behaviour and to check simulation results (see e.g.

Erickson et al., 2010).

The outcome of the analysis or computer simulation then have to be interpreted and compared with the real world. Most often, the comparison will reveal that some stages of the modelling process need further adjusting (often all of them). All in all, the successful modelling approach will depend on the model design, the parametrisation, the validity of input data and in part on the modeller's experience (Boumans, 2005).

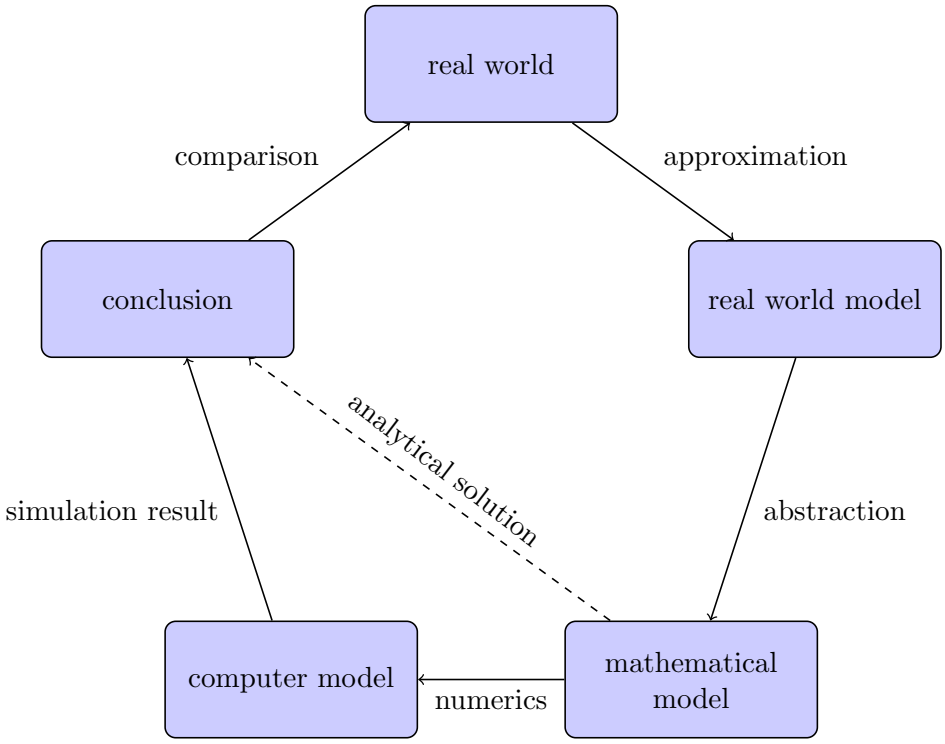

Figure 1.4: Mathematical modelling. A representation of a real world process can be accomplished by using a sequence of abstraction levels. The output of the resulting model then has to be compared to the real process and, if it is not sufficiently close, the abstraction steps have to be refined.

Parametrisation

Parameters of the model determine the transitions of variables from one time step to the next. The parametrisation of the model, that is the choosing and defining of parameters, happens at the step from real world model to the mathematical one. Constant parameters are assigned specific values and the varying parameters are assigned response curves, for example to describe development in response to temperature.[5] Most often, there are several function types available to select from for response curves, depending on fitting techniques and biological justification.

[5]Technically, model parameters are constants, while model variables can vary, for example depending on temperature. However, to distinguish between quantities that are determined at the start of the analysis, and those that are not, we will only refer to the latter as variables and the first as parameters. For example, we can compute a varying, temperature-dependent mortality rate for the whole period of interest at the start of the analysis or simulation, using the given temperature data, but we would classify it as parameter to distinguish it from variables such as the number of mosquito larvae or disease incidents.

Examples are the shape of virus incubation rates (Chan and Johansson, 2012) or the shape of mortality curves (Wilson, 1994, for fruit flies). Most often, statistical models are used to fit regression curves to data (see e.g. Rubel et al., 2008; Chen et al., 2012).

Obviously, both constant and varying parameters are only as good as the data they are derived from. If we wanted to model for example mosquito development in the field, it would be best to use data from field studies to estimate development, mortality or fecundity rates. However, extensive field study data are not frequently available and often cannot be generalised due to a lack of controlled conditions. Instead, meta-analyses (Brady et al., 2013) or laboratory studies (Lee, 1994; Delatte et al., 2009) are often the basis for parameter estimations. Some parameters have to be estimated by the modeller though as they lack any experimental basis for ethical reasons, for example the transmission probability of diseases from vector to human.

1.3.2 Climate Data

As described earlier, various climate factors influence mosquitoes and pathogen transmission. The climate factor that often has the greatest impact on mosquito development and pathogen transmission is temperature, followed by precipitation or rainfall (Kraemer et al., 2015; Cunze et al., 2016). Other climate factors, including humidity (Rudolfs, 1925; Yamana and Eltahir, 2013), photoperiod (Pumpuni et al., 1992; Xia et al., 2018) or wind (Service, 1980; Takahashi et al., 2005), can impact the population dynamics too.

If mosquito development is modelled only at one location for a certain time of year, constant climate and thus constant model parameters can be assumed. Examples include works for dengue transmission in Thailand (Chanprasopchai et al., 2018) or malaria in India (Martcheva and Hoppenstaedt, 2010). Though the parameters in these models are adjusted to the according climates, the models themselves are climate-independent. But as soon as we look at locations that experience seasonal cycles with warm and cold or wet and dry seasons, we need climate-dependent parameters, such as rates for larval development or adult mortality. These models can either be used for specific locations over longer time periods (Erickson et al., 2010; Tran et al., 2013) or for multiple locations up to whole regions (Jia et al., 2016; Erguler et al., 2016).

The data used to drive these models are usually weather station data with recordings for point locations, or gridded climate data that have been processed from weather station (e.g. APHRODITE and CRU TS, Yatagai et al., 2012; Harris et al., 2014) or satellite data (e.g. TRMM, Del Genio, 2013). Gridded future climate predictions are based on climate models, driven by carbon emission scenarios (e.g. NEX-GDDP, Thrasher et al., 2012). Data sets are often supplied for download in CSV, ASCII or NetCDF format and can be transformed into the desired file format, time period, resolution and coordinates with programming suites such as *cdo* (Schulzweida, 2019) or *Python* (Oliphant, 2007).

In our model simulations, we calculate the rate of change of mosquito or infection dynamics with the climate data as drivers. In simplified terms, we load temperature, rainfall and other inputs

to first calculate model parameters such as temperature-dependent mortality rates for a specific location and time. The model is evaluated at this particular time step and the whole process is repeated for the next time step, see Figure 1.5. When we make calculations for whole areas, we have to load the climate data into two-dimensional matrices but the calculation process stays the same. Mathematically speaking, the model consists of multivariate matrix functions, mapping $\mathbb{R}^{2n} \rightarrow \mathbb{R}^2$ for n inputs. *GNU Octave v4.2.1* (`https://www.gnu.org/software/octave/`), which is the freeware equivalent to *MatLab*, is used for calculations, with packages *ncarray* and *netcdf*, as this programming language is highly suitable for matrix handling (Eaton et al., 2016).

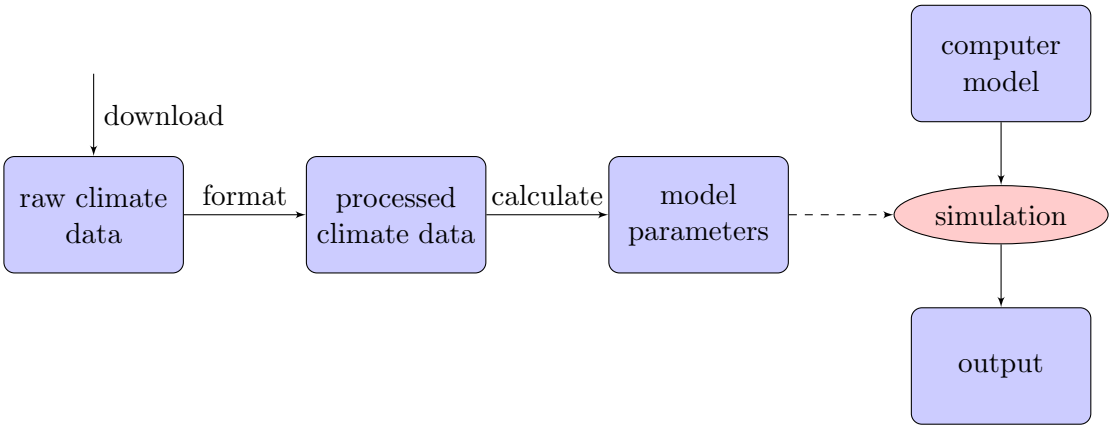

Figure 1.5: Climate Data. The use of climate data as drivers in vector and transmission risk modelling.

Note that not all input parameters have to be climate-dependent. An important factor in vector modelling is for example the availability and quality of mosquito breeding sites. Apart from rainfall, these can be estimated by vegetation indices for woodland or coastal species (Brown et al., 2008) or by human population density data for species that have adapted to urban areas and breed in artificial containers (Obenauer et al., 2017). However, there is no difference in data handling compared to climate-dependent data.

1.3.3 Summary

The last decades have seen a steep increase in the number of models for mosquito-borne pathogen transmission (Reiner et al., 2013). Climate factors, playing a key role in mosquito development and pathogen transmission, are frequently used as model drivers. These models can reveal epidemiological patterns of disease distribution and spread that can help public health officials to decide on the timing, place, and extent of interventions and countermeasures (Heesterbeek et al., 2015).

1.4 Summary of Aims

Currently, there are 36 mosquito species present in the UK but only a couple are numerous enough and capable of transmitting viruses or other pathogens to humans. But the biggest threat to public health might be yet to come; a species that is only on the verge of establishing in the UK: the Asian tiger mosquito *Ae. albopictus*. A comparison with Italy shows why this mosquito is such a big threat: Similar to the UK, Italy had a high burden of malaria until the early-mid 20^{th} century (Dobson, 1980; Majori, 2012). After eradication programmes it was practically malaria free and today there are only very few cases of malaria in Italy (Benelli et al., 2018) despite endemic *Anopheles* vector species (Jetten and Takken, 1994; Baldari et al., 1998). Italy does, however, have bigger outbreaks of chikungunya, even though malaria cases are introduced at a six-fold rate (ECDC, 2018*a*, 2019). We would argue that this is due to *Ae. albopictus*. This vector species can reach high numbers in summer months and is a frequent human biter, somewhat adapted to areas with high human density.

The UK, albeit cooler than Italy, could suffer the same fate in the future. Studies analysing *Ae. albopictus*' ecological niche indicate that the UK is already suitable for this species, but disagree where and to what extent (Fischer et al., 2011; Caminade et al., 2012; Kraemer et al., 2015; Erguler et al., 2016). We thus decided to concentrate on *Ae. albopictus* as vector species in our mosquito-borne diseases studies. We use a range of mathematical models, mostly deterministic differential equation, to analyse this mosquito, its potential spread to the UK, and its emanating risk of pathogen transmission.

In **chapter 2**, we develop an ODE model for the life cycle of *Ae. albopictus* and validate it with European mosquito occurrence and larval index data. We use historical climate data sets to analyse the UK's current suitability for this mosquito species, before we use climate projections for the UK's future suitability under different carbon emission scenarios.

In **chapter 3**, we analyse the spread of *Ae. albopictus* in Europe using a PDE model. We use our findings to simulate an introduction of this mosquito into the UK with subsequent spread during the next 30 years.

In **chapter 4** and **chapter 5**, we model mosquito-borne disease risk in countries where *Ae. albopictus* has already established, namely China and countries of Latin America. We develop a DDE model and use an R_0 model to investigate climatic impacts on several disease outbreaks to estimate arbovirus transmission risk in Europe.

In **chapter 6**, we compare the development and survival of European and tropical strains of *Ae. albopictus* in a laboratory experiment. We use a range of low temperature settings to test if larvae, pupae or adult females of the European strain show cold-adaptations that would enable them to cope with temperate UK climates.

With these works, this thesis aims to answer the main questions:

- Could the vector species *Ae. albopictus* become established in the UK?
- If it can survive in the UK, where would that be and in what numbers?
- Given its implication in disease transmission elsewhere, would it pose any threats to public health in the UK?

Chapter 2

The UK's suitability for *Aedes albopictus* in current and future climates

The Asian tiger mosquito *Aedes albopictus* is able to transmit various pathogens to humans and animals and it has already caused minor outbreaks of dengue and chikungunya in southern Europe. Alarmingly, it is spreading northwards and its eggs have been found in the UK in 2016 and 2017. Climate-driven models can help to analyse whether this originally sub-tropical species could become established in northern Europe. But so far, these models have not considered the impact of the diurnal temperature range (DTR) experienced by mosquitoes in the field. Here, we describe a dynamical model for the life cycle of *Ae. albopictus*, taking into account the DTR, rainfall, photoperiod and human population density. We develop a new metric for habitat suitability and drive our model with different climate data sets to analyse the UK's suitability for this species. For now, most of the UK seems to be rather unsuitable, except for some densely populated and high importation risk areas in south-east England. But this picture changes in the next 50 years: future scenarios suggest that *Ae. albopictus* could become established over almost all of England and Wales, indicating the need for continued mosquito surveillance.

2.1 Introduction

About ten invasive species become established in Europe each year (Hulme, 2009) and the UK alone spends about £1.7 billion annually to mitigate their impacts (Williams et al., 2010). One of these species that has already invaded Europe and might now spread to the UK is the Asian tiger mosquito, *Ae. albopictus*. This mosquito spreads worldwide through its long-lasting and drought-resistant eggs that can be transported over long distances, for example in used vehicle tyres or lucky bamboo pot plants (Vaux and Medlock, 2015). The eggs can also undergo a diapause to resist colder winter temperatures (Lacour et al., 2015), allowing temperate regions significantly colder than its original niche in South East Asia to be colonised. In Europe, *Ae. albopictus* was introduced in the late 1970s to Albania (Adhami and Reiter, 1998), in 1990 to Italy (Sabatini et al., 1990) and more recently into the Netherlands (Scholte et al., 2008). Since its introduction into Italy, it has rapidly spread along the Mediterranean coast and is now expanding its northern range (ECDC Vectornet, 2019).

This is a major concern as *Ae. albopictus* is an effective disease vector. It can transmit a range of arboviruses affecting humans and animals, including chikungunya, dengue and Zika viruses (Grard et al., 2014), as well as filarial worms (Gratz, 2004). In Europe, it was responsible for two outbreaks of chikungunya in Italy and a few cases of dengue in Croatia and France in the last ten years (Rezza et al., 2007; Schaffner and Mathis, 2014; Venturi et al., 2017). In addition, it is a potent vector of zoonotic diseases because it feeds on mammals, birds, reptiles, and amphibians (Niebylski et al., 1994), although it feeds preferentially on humans in urban areas (Kamgang et al., 2012). So whether or not *Ae. albopictus* will spread from continental Europe to the UK and subsequently become established is of significant public health interest. And there is evidence for recent introductions: in September 2016, eggs were found in Kent, the English county closest to France, by a surveillance team of Public Health England (Medlock et al., 2017), followed by another finding of eggs and larvae in July 2017 at another site in the same county (PHE, 2017). Here, gravid females have probably been carried over in cars or lorries and subsequently laid eggs when released at motorway service points.

Static and statistical niche models have been developed to analyse the UK's climatic suitability for *Ae. albopictus*, suggesting that large parts of southern England are already suitable (Medlock et al., 2006; Fischer et al., 2011; Caminade et al., 2012). Dynamical models, better suited to capture the non-linear behaviour of the mosquito's development, have been published more recently (Erickson et al., 2010; Tran et al., 2013; Jia et al., 2016; Erguler et al., 2016). While all of these models use seasonal or daily mean temperatures and rainfall as drivers, it has become clear that the diurnal temperature range (DTR) significantly affects the life cycle of insects too. The DTR is the difference between the maximum temperature during the day and the minimum night-time temperature. Studies on *Aedes* mosquitoes show that rates for development and mortality differ substantially under constant temperature conditions compared with a realistic diurnal temperature cycle (Mohammed and Chadee, 2011; Richardson et al., 2011; Carrington et al., 2013). Models that already incorporate a DTR have been developed for aphids (Ma et al., 2015), moths (Chen et al., 2015), generic insects (Vasseur et al., 2014) and its ef-

fect have been recently applied to a model for *Anopheles* mosquitoes (Beck-Johnson et al., 2017).

Here, we describe the development of a novel dynamical model for *Ae. albopictus* that explicitly incorporates the effect of DTR on its life cycle. We use mosquito occurrence data and container index data to evaluate the model performance before analysing the suitability of the UK for this invasive mosquito under current climate conditions and under two climate projection scenarios for the future.

2.2 Model & Methods

Based on previous studies, we chose a compartmental, climate-driven approach to model the life cycle of *Ae. albopictus* (Erickson et al., 2010; Jia et al., 2016; Erguler et al., 2016). The model comprises five differential equations. Details on climate-dependent variables can be found in appendix A2.1.

2.2.1 Dynamic Life Cycle Model

The mosquito life cycle is described by five mosquito classes: normal, non-diapausing eggs E, juvenile aquatic stages J, immature female adults I, mature female adults A, and diapausing eggs E_d (Figure 2.1). Normal, non-diapausing eggs are laid during summer by mature females with a rate of $\beta\,(1-\omega)$. Larvae are ready to hatch after eggs complete a development period with a rate of δ_E, and are activated with a probability h by rainfall and artificial irrigation. The four larval stages and the pupal stage are combined into a single aquatic juvenile class in the model. Assuming a sex ratio of 50:50, juveniles then develop into newly eclosed male and female adults with the rate δ_J. Newly eclosed female mosquitoes do not directly show host seeking behaviour. Instead, they first spend some time in a resting stage, only after which they mature with a rate of δ_I and take their first blood meal to start laying eggs (Delatte et al., 2009).

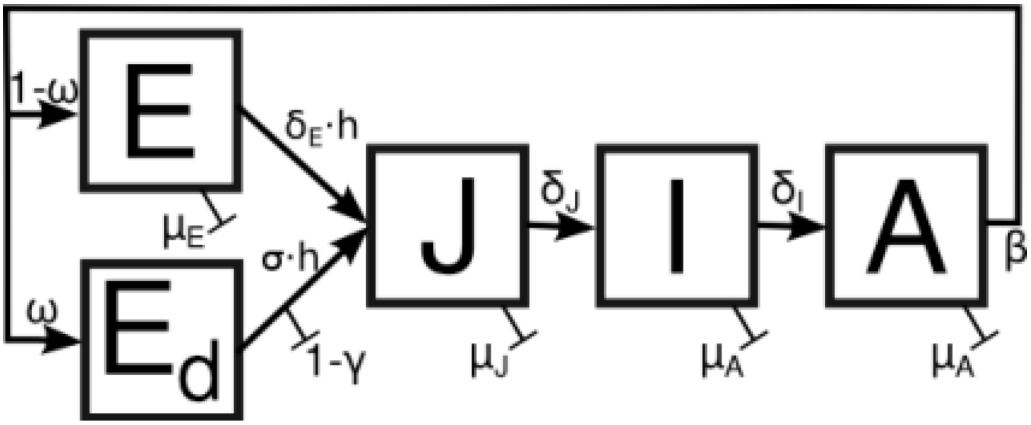

Figure 2.1: ODE model life stages of *Ae. albopictus* Eggs E hatch and become juveniles J (larvae and pupae). They develop to newly eclosed (immature) females I and finally to mature female adults A. Adult female mosquitoes lay normal eggs E in the summer months or diapausing eggs E_d at the end of the season. Diapausing eggs overwinter and are activated by a combination of longer day lengths, warmer temperatures and rainfall in spring.

At the end of the season, the egg laying process depends on the photoperiod, P. When days are getting shorter, females start to lay diapausing eggs with a rate of $\beta\,\omega$ that do not hatch after a few days but overwinter. During the following spring, these eggs are ready to hatch when temperatures and photoperiod reach critical thresholds, and are eventually activated by rainfall with a probability h.

All transitions from one class to another depend on temperature, T, and so do mortality rates μ. Because *Ae. albopictus'* water filled breeding sites are usually small (Paupy et al., 2009), we

use air temperature as a proxy for water temperature.

With parameter definitions given in Table 2.1, model equations are as follows:

$$
\begin{aligned}
\tfrac{d}{dt}E(t) &= \beta\,(1-\omega)\,A(t) - h\,\delta_{\mathrm{E}}\,E(t) - \mu_{\mathrm{E}}\,E(t)\\
\tfrac{d}{dt}J(t) &= h\,\delta_{\mathrm{E}}\,E(t) + h\,\sigma\,\gamma\,E_{\mathrm{d}}(t) - \delta_{\mathrm{J}}\,J(t) - \mu_{\mathrm{J}}\,J(t) - \frac{J(t)^2}{K}\\
\tfrac{d}{dt}I(t) &= \tfrac{1}{2}\,\delta_{\mathrm{J}}\,J(t) - \delta_{\mathrm{I}}\,I(t) - \mu_{\mathrm{A}}\,I(t)\\
\tfrac{d}{dt}A(t) &= \delta_{\mathrm{I}}\,I(t) - \mu_{\mathrm{A}}\,A(t)\\
\tfrac{d}{dt}E_{\mathrm{d}}(t) &= \beta\,\omega\,A(t) - h\,\sigma\,E_{\mathrm{d}}(t)
\end{aligned}
$$

The development from juvenile to immature females is halved in the equation for $\frac{d}{dt}I(t)$, $\frac{1}{2}\delta_J$, to account for the 50:50 sex ratio. The squared term $\frac{J^2}{K}$ in the juvenile equation describes negative density dependence[1]. Development rates, δ, and mortality rates for eggs and juveniles, μ_{E} and μ_{J}, depend on the actual oscillating diurnal temperature T. Only the mortality rate for adults is derived from field data that already include a DTR. Daily mean temperatures, T_{mean}, are therefore used for μ_{A}. T_7 is the average temperature over the recent seven days, used to trigger the spring hatching rate.

Due to the lack of information regarding the survival rates of eggs over long time periods (several months), we assume a survival probability γ of diapausing eggs that is dependent on the minimum winter temperature experienced, $T_{\mathrm{DJF,min}}$. The survival probability is applied when eggs are activated in spring, see appendix A2.1 for details. Remaining diapausing eggs that have not hatched until August are removed.

Larval mortality not only depends on temperature, but also on an environmental carrying capacity, K. We use the model by White et al. (2011) and its extension by Erguler et al. (2016) to calculate K from rainfall, R, and human population density, H:

$$
K(R,H) = \lambda \frac{1-\alpha_{\mathrm{evap}}}{1-\alpha_{\mathrm{evap}}^{t}} \sum_{x=1}^{t} \alpha_{\mathrm{evap}}^{(t-x)} \left(\alpha_{\mathrm{rain}}\,R(x) + \alpha_{\mathrm{dens}}\,H(x)\right), \tag{2.1}
$$

This carrying capacity equation describes the formation of water bodies either by rainfall or by (constant) artificial irrigation, and the subsequent shrinking of these water bodies by evaporation, see Figure 2.2. The water bodies represent the living space of larvae and pupae. When they increase in volume, the density of juveniles decreases and with it the competition and predation among them (Briegel and Timmermann, 2001). As we model mosquito abundance in individuals per hectare, we keep the parameters at $\alpha_{\mathrm{evap}} = 0.9, \alpha_{\mathrm{dens}} = 0.001\,km^2$, and $\alpha_{\mathrm{rain}} = 0.00001\,mm^{-1}$ (Erguler et al., 2016) but multiply by a scaling factor λ to reach a max-

[1] This negative density dependence was first described in (a slightly different) form of the logistic population equation $N_{t+1} = rN_t(1-\frac{N_t}{K}) = rN_t - \frac{N_t^2}{K}$ by Verhulst (1838). It describes a slower population growth the closer the population gets to its carrying capacity, K, respectively a population shrinkage if the population size is higher than K. In our compartmental model, the juvenile class does not reproduce itself, so that we use eggs E and E_{d} as inputs instead of rN_t.

Table 2.1: ODE model parameters Derivation and references of parameters are shown in appendix A2.1. Environmental drivers are temperature, T, rainfall, R, photoperiod, P, latitude, L and human population density, H. Please note that the environmental carrying capacity, K, and the egg activation by rainfall, h, are defined in equations (2.1) and (2.2).

	Parameter	**Value/Formula**
$\mathrm{CTT_S}$	Critical temperature over one week in spring (°C)	$11.0^{\star}$
$\mathrm{CPP_S}$	Critical photoperiod in spring (hours)	$11.25^{\star}$
$\sigma(T,P)$	Spring hatching rate (1/day)	$\begin{cases} 0 & \text{if } T_7 < \mathrm{CTT_S} \text{ or } P < \mathrm{CPP_S} \\ r_S = 0.1^{\dagger} & \text{if } T_7 \geq \mathrm{CTT_S} \text{ and } P \geq \mathrm{CPP_S} \end{cases}$
$\mathrm{CPP_A}(L)$	Critical photoperiod in autumn (hours)	$10.058 + 0.08965\,L$
$\omega(P)$	Fraction of eggs going into diapause	$\begin{cases} 0 & \text{if } P > \mathrm{CPP_A} \text{ or } t < 183 \\ r_A = 0.5 & \text{if } P \leq \mathrm{CPP_A} \text{ and } t \geq 183 \end{cases}$
δ_E	Normal egg development rate (1/day)	$1/7.1$
$\delta_J(T)$	Juvenile development rate (1/day)	$1/(83.85 - 4.89\,T + 0.08\,T^2)$
$\delta_I(T)$	First pre-blood meal rate (1/day)	$1/(50.1 - 3.574\,T + 0.069\,T^2)$
$\mu_E(T)$	Egg mortality rate (1/day)	$-\ln(0.955\,\exp(-0.5\,(\frac{T-18.8}{21.53})^6))$
$\mu_J(T)$	Juvenile mortality rate (1/day)	$-\ln(0.977\,\exp(-0.5\,(\frac{T-21.8}{16.6})^6))$
$\mu_A(T_{\mathrm{mean}})$	Adult mortality rate (1/day)	$-\ln(0.677\,\exp(-0.5\,(\frac{T_{\mathrm{mean}}-20.9}{13.2})^6)\,T_{\mathrm{mean}}^{0.1})$
$\gamma(T_{\mathrm{DJF,min}})$	Survival probability of diapausing eggs (1/winter)	$0.93\,\exp(-0.5\,(\frac{T_{\mathrm{DJF,min}}-11.68}{15.67})^6)$
$\beta(T)$	Egg laying rate (1/day)	$\begin{cases} 33.2\,\exp(-0.5\,(\frac{T-70.3}{14.1})^2)\,(38.8-T)^{1.5} & \text{if } T \leq 38.8 \\ 0 & \text{if } T > 38.8 \end{cases}$
λ	Capacity parameter (larvae · days /hectare)	10^6 ‡

⋆ Toma et al. (2003), † Best estimate, ‡ Tran et al. (2013); Cailly et al. (2012)

imum carrying capacity ranging between 500,000 and 800,000 individuals per hectare (Tran et al., 2013; Cailly et al., 2012).

Similar to the carrying capacity, we model the probability of eggs hatching to depend on rainfall and human population density. We use the rainfall-dependent approach by Abdelrazec and Gumel (2017) and assume that up to $\epsilon_{\mathrm{rat}} = 20\%$ of eggs can hatch in densely populated areas regardless of rainfall conditions:

$$h(R,H) = (1-\epsilon_{\mathrm{rat}})\,\frac{(1+\epsilon_0)\exp(-\epsilon_{\mathrm{var}}\,(R(t)-\epsilon_{\mathrm{opt}})^2)}{\exp(-\epsilon_{\mathrm{var}}\,(R(t)-\epsilon_{\mathrm{opt}})^2)+\epsilon_0} + \epsilon_{\mathrm{rat}}\,\frac{\epsilon_{\mathrm{dens}}}{\epsilon_{\mathrm{dens}}+\exp(-\epsilon_{\mathrm{fac}}\,H(t))}. \tag{2.2}$$

We set the optimal amount of daily rainfall to $\epsilon_{\mathrm{opt}} = 8\,mm$, and use $\epsilon_0 = 1.5$ and $\epsilon_{\mathrm{var}} = 0.05\,mm^{-2}$ (Abdelrazec and Gumel, 2017). Density dependent parameters are set to $\epsilon_{\mathrm{dens}} = 0.1$ and $\epsilon_{\mathrm{fac}} = 0.01\,km^2$, such that egg hatching is increased in areas where $H > 500$ people per km^2. The response curve to rainfall is depicted in Figure 2.3.

The photoperiod, that is the length of the period from sunrise to sunset, is calculated using the daylight model by Forsythe et al. (1995). Assuming sunrise/sunset takes place when the centre

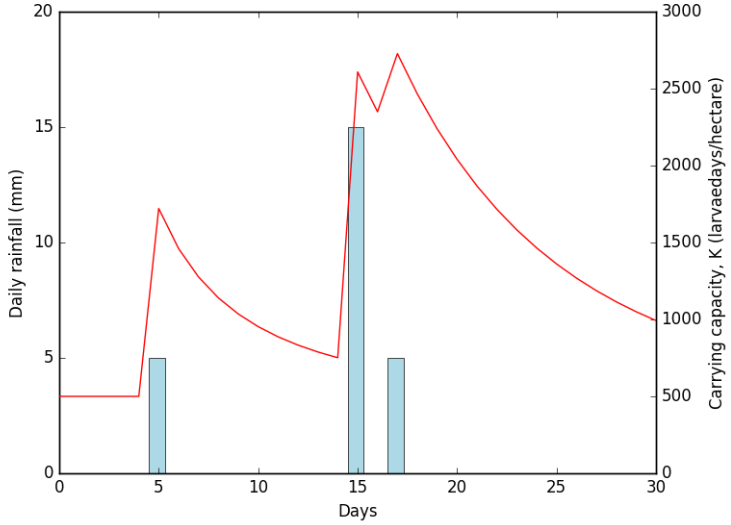

Figure 2.2: Carrying capacity The red line shows the juvenile carrying capacity that increases with rainfall (blue bars) and decreases over time with evaporation. In the presence of humans, the carrying capacity does not fall to zero, reflecting artificial irrigation. Here, the human population density was set to 50 ind./km^2.

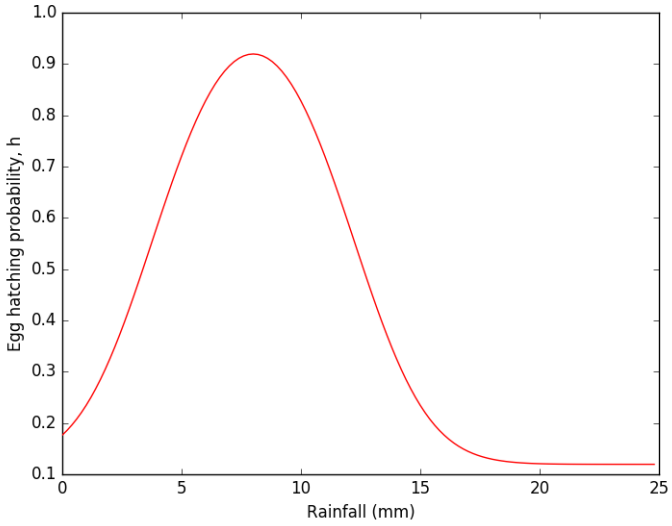

Figure 2.3: Hatching probability The hatching probability of eggs depends on rainfall and the human population density. If it is too dry, not many eggs will hatch, if it is too rainy, too many eggs (and newly hatched larvae) get flushed away. A small proportion will always hatch due to human activity, human population density was set to 500 ind./km^2.

of the sun is even with the horizon, the photoperiod, P, is given by

$$\begin{aligned}
\theta &= 0.2163108 + 2\,\tan^{-1}(0.9671396\,\tan(0.0086\,(\mathrm{DOY} - 186))) \\
\phi &= \sin^{-1}(0.39795\,\cos(\theta)) \\
P &= 24 - \frac{24}{\pi}\cos^{-1}\left(\frac{\sin(\frac{\pi L}{180})\,\sin(\phi)}{\cos(\frac{\pi L}{180})\,\cos(\phi)}\right).
\end{aligned} \tag{2.3}$$

with DOY being day of year, ranging from 1 to 365, and L for latitude in decimal degrees.

Note that other studies split the juvenile stage into larvae and pupae stages and some also split the mature female stage into host seeking, gestating, and ovipositing stages (see e.g. Tran et al., 2013; Erguler et al., 2016; Jia et al., 2016). We also simulated these scenarios but they did not improve model fit to presence or container index data. As there was more parametrisation data available for a reduced model, we kept the model framework with a minimum number of equations. See A2.2 for further details.

Runge-Kutta 4 is used to solve ODEs, further details on the numerics are given in appendix A2.3.

Suitability index

We propose a suitability index E_0 that relates to the basic reproduction number R_0 in epidemiological studies. In epidemiology, R_0 is defined by the number of susceptibles infected by a single infectious individual in an otherwise uninfected (susceptible) population. Accordingly, we define our suitability index by the number of eggs that are produced at the end of a year, after placing a single (diapausing) egg at the beginning of the year into an uncolonised location. The amount by which the number of eggs has increased (suitable) or decreased (unsuitable) defines the suitability index E_i of that year i. Repeating this procedure for n consecutive years and taking the geometric mean of the yearly suitability indices gives the suitability index, E_0, for the according period,

$$E_0 = \sqrt[n]{\Pi_{i=1}^{n} E_i},$$

with $E_i = \dfrac{E_\mathrm{d}(\mathrm{day} = 365)}{E_\mathrm{d}(\mathrm{day} = 1)}$. Note that the crucial scaling of E_0 depends on the carrying capacity, K. With our standard settings, the model predicts about 1 200 adult female *Ae. albopictus* per hectare for August/September in Rome, see Figure 2.16. This is well in the range of mark-release-recapture data, with an estimated 1 400 females per hectare (Marini et al., 2010). See A2.4 for further details on advantage and limitations of this index.

Diurnal temperature cycle

To calculate the DTR, we use the model by de Wit (1978), which is well suited to compute realistic temperatures throughout the day from maximum and minimum temperatures (Reicosky et al., 1989). Time points for temperature calculation are chosen according to the time steps for our explicit numerical solver, e.g. if $k = \frac{1}{100}$, we calculate 100 actual temperatures throughout the day at 00:14, 00:19, ... 24:00. Temperatures during day i are calculated by

$$T_i(h_t) = \begin{cases} \frac{T_{i-1}^{\max}+T_i^{\min}}{2} + \frac{T_{i-1}^{\max}-T_i^{\min}}{2}\cos(\frac{h_t+10}{10+t_\mathrm{s}}\pi) & \text{if } h_t < t_\mathrm{s} \\ \frac{T_i^{\max}+T_i^{\min}}{2} - \frac{T_i^{\max}-T_i^{\min}}{2}\cos(\frac{h_t-t_s}{14-t_\mathrm{s}}\pi) & \text{if } t_\mathrm{s} < h_t < 14 \\ \frac{T_i^{\max}+T_{i+1}^{\min}}{2} + \frac{T_i^{\max}-T_{i+1}^{\min}}{2}\cos(\frac{h_t-14}{10+t_\mathrm{s}}\pi) & \text{else} \end{cases}$$

with $T_i^{\max\,/\,\min}$ being the maximum or minimum temperature of day i. The model assumes

$T^{\min}$ at sunrise t_s and $T^{\max}$ at 14:00 local time. The time of day in hours is given by h_t. The time of sunrise, t_s, is approximated by assuming that the daylight photoperiod calculated with equation (2.3) is centred around noon, such that

$$t_s = \frac{12}{\pi} \cos^{-1} \left(\frac{\sin(\frac{\pi L}{180}) \sin(\phi)}{\cos(\frac{\pi L}{180}) \cos(\phi)} \right).$$

Climate and Population Density Data

We run our model with a range of different climate data sets from historical records and future climate projections. For mosquito suitability in the UK, we compare the observed gridded climate data sets from E-OBS on a 25 km × 25 km spatial scale (Haylock et al., 2008) and from UKCP09 on a 5 km × 5 km scale (Jenkins et al., 2009). The E-OBS data set is used for model validation over Europe and the ERG5 Eraclito data set (Antolini et al., 2016) is used for the model runs in the Emilia-Romagna region.
For future model runs across Europe, we use 25 km × 25 km spatial scale climate projections from the NASA NEX-GDDP project (Thrasher et al., 2012) for two different emission scenarios (Representative Concentration Pathways), the median RCP4.5 and the extreme RCP8.5 scenario. A subset of 5 out of 21 general circulation models was chosen to represent the full range of uncertainty, see A2.5 for details. For future changes, we focus on the period 2060 – 2069, the 2060s hereafter.

Human population density is based on the GPWv4 data set (Doxsey-Whitfield et al., 2015). For the 2060s projections, we assume the total UK population has increased from 65.5 million to 75 million (ONS, 2017) but has not changed in its spatial distribution.

2.2.2 Validation

Presence data

To validate the spatial distribution of suitability simulated by the model, we used *Ae. albopictus* occurrences (Kraemer et al., 2015), updated with data from recent literature (Akiner et al., 2016; Walther et al., 2017; Di Luca et al., 2017; Medlock et al., 2017; PHE, 2017; Osório et al., 2018), and classified into established populations and one-time sightings according to the 2019 ECDC classification (ECDC Vectornet, 2019). Occurrence points that were less than 25 km apart from one another were clustered together, resulting in a total of 234 out of 385 data points. We then checked whether each established occurrence point fell into a grid cell that was calculated to be suitable ($E_0 \geq 1$) or unsuitable ($E_0 < 1$).

Figure 2.4 shows the suitability index for the period 2006 – 2016, which is highly consistent with occurrence data: 83% of the established populations fall into a suitable grid cell, 17% into unsuitable ones (excluding grid cells that are not covered by climate data). The model predicts very unsuitable conditions in Northern Europe, where the mosquito is absent, and in large parts of Eastern Europe, where a strong continental winter leads to unsuitable conditions (Cunze et al., 2016). For example, *Ae. albopictus* had been introduced multiple times into the

Czech Republic (clustered together in Figure 2.4) but was not able to establish (Rudolf et al., 2018).

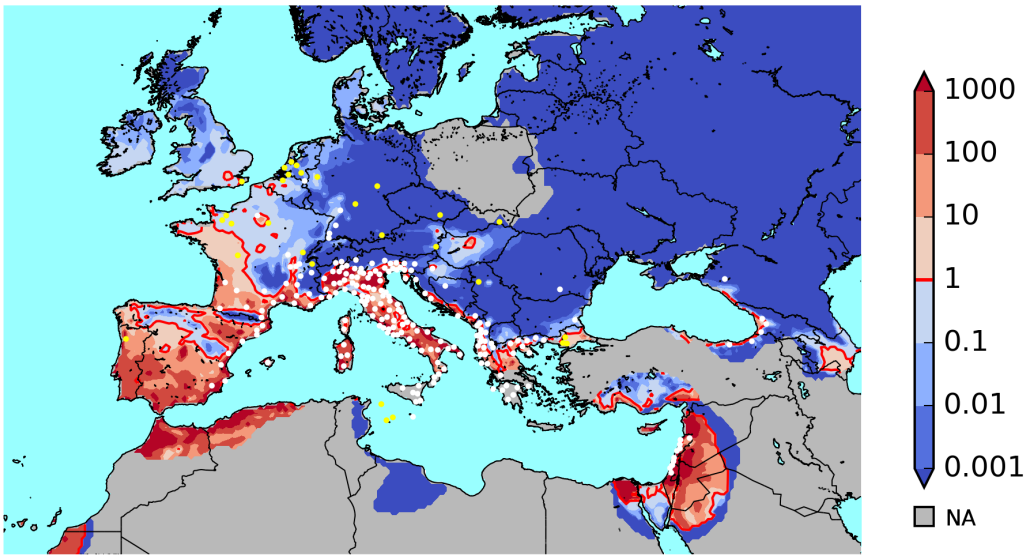

Figure 2.4: Spatial validation for Europe's suitability White dots show established *Ae. albopictus* populations, yellow dots show one-time sightings. Background colours show the simulated suitability index of the period 2006 to 2016. Red contour distinguishes suitable ($E_0 > 1$) from unsuitable areas ($E_0 < 1$). In the grey area, climate data from the E-OBS data set was incomplete for all years of the study period.

However, the model misses some points in the southern Alps, the Bulgarian/Romanian Black Sea coast and some southern German cities. This is possibly because occurrences fall into warmer valleys or urban areas with microclimate conditions that are not captured by the coarse spatial resolution of the climate data (Werner and Kampen, 2015). The model predicts suitable conditions for areas such as southern Germany in most years but specific years with a very cold winter or dry summer lower the 10-year suitability index. Figure 2.5 shows the suitability for 2016 only. The suitability over Western Europe (UK, France, Benelux, Germany) is higher than the 10-year mean.

More densely populated areas, such as Madrid, Paris and London appear as suitable; they act as heat islands, further increasing mosquito development (Meineke et al., 2013), and they supply mosquito breeding sites by man-made containers and irrigation.

We also performed a Receiver Operating Characteristic (ROC) analysis. Varying the discriminatory threshold of the suitability index (currently the threshold is at 1 egg at the end of the year for one egg at the start of the year) shows the possible and the realised predictive ability of the model. The ROC identifies the simulated suitability index' sensitivity, i.e. how many occurrence points are correctly identified as suitable, and specificity, i.e. how many places without mosquito occurrence get identified as unsuitable. As there is only presence data available, we had to introduce pseudo-absence data for the mosquito. We assume that the mosquito is absent from all grid cells without any occurrence recordings and randomly choose the same number of

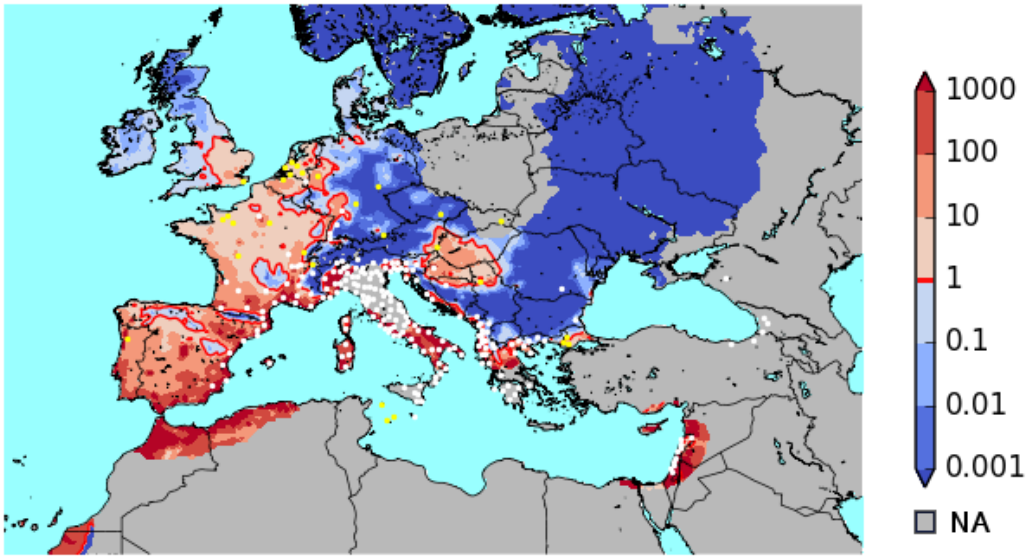

Figure 2.5: Europe's suitability 2016 White dots show established *Ae. albopictus* populations, yellow dots show one-time sightings. Background colours show the simulated suitability index for 2016 only. Red contour distinguishes suitable ($E_0 > 1$) from unsuitable areas ($E_0 < 1$). The E-OBS climate data set was incomplete for 2016, so that northern Italy and areas around the Black Sea appear grey.

absence points as there are presence points (Barbet-Massin et al., 2012). The random sampling is repeated 10 times and the average is taken on output measures.

We found that the suitability classification with a threshold of $E_0 = 1$ is working well for the European data (an optimal threshold would be $\tilde{E}_0 = 1.001$), see Figure 2.6. The probability of a region with mosquito occurrence getting a higher value than one without is given by the area under the curve (AUC) value (Fawcett, 2006) and we get an AUC of 0.9 for the mean of the ten-year prediction in Figure 2.4.

Container Index data

To validate the temporal population dynamics, Italian container index (CI) data of *Ae. albopictus* eggs were used for the period 2011 – 2015 (Carrieri et al., 2011). The region of Emilia-Romagna has nine districts and each district is monitored for *Ae. albopictus* eggs by ovitraps that are checked and numbers are counted on a biweekly basis.

We run our model with Emilia-Romagna climate data for the period 2010 – 2015 to have one year of spin-up (cell codes 01421, 01867, 01699, 01138, 00369, 00774, 01983, 00977, 02231 for the according region). Figure 2.7 shows the comparison between the empirical CI data and scaled simulated egg data over a period of five years in the according region. Pearson's correlation coefficient for simulated vs. empirical egg data for individual regions range from $r = 0.54$ for Reggio-Emilia to $r = 0.86$ for Bologna, with an overall correlation of $r = 0.70$ (95% CI: $0.67 \leq r \leq 0.73$, N=996).

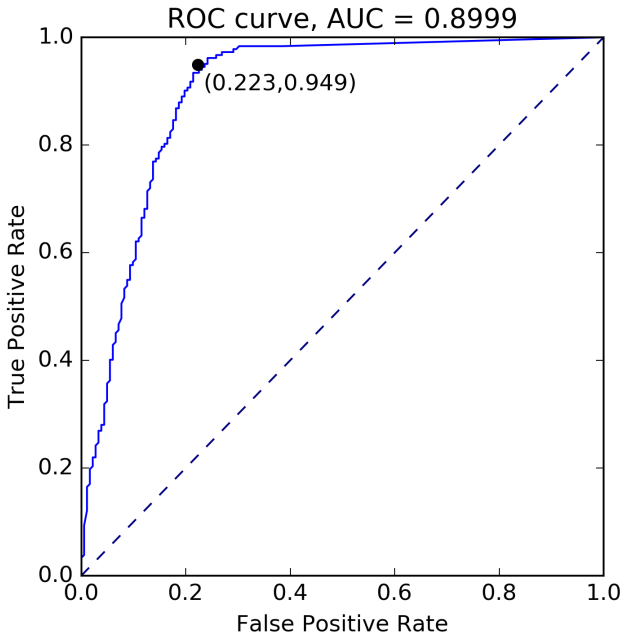

Figure 2.6: ROC for Europe Receiver operating characteristic curve. The black dot represents Youden's index, the best compromise between specificity (1-FPR) and sensitivity (TPR). The area under the curve (AUC) gives the probability of a region with mosquito occurrence getting a higher suitability index than one without.

In addition, we look at the upper tercile (highest 33% of all biweekly values over all nine regions) and upper decile (highest 10%) of CI data and model outputs. The upper tercile indicates the main mosquito season while the upper decile indicates the highest peaks. Figure 2.8 shows that the model captures the main seasonality quite well, onset and end match approximately for observed and simulated numbers. However, the model overestimates the peak mosquito numbers in the years 2011 and 2014, while it underestimates peak mosquito numbers in 2015. This discrepancy is mainly due to 2014 showing very suitable spring temperatures and abundant rainfall in summer, while 2015 does not (not shown). The true skill statistic (TSS) is the most suitable score to evaluate model (forecast) accuracy (Woodcock, 1976) and defined by

$$\mathrm{TSS} = \frac{\mathrm{TP}}{\mathrm{TP+FN}} - \frac{\mathrm{FP}}{\mathrm{FP+TN}},$$

with TP being true positives, etc. We get a TSS = 0.82 for upper terciles and TSS = 0.42 for upper deciles categories.

Sensitivity analysis

To investigate the influence of each parameter on the final model output, E_0, we perform the elementary effects test (EET) as suggested by Morris (1991). In the EET, single input parameters X are varied and a simulation is run, resulting in the model output Y. An elementary

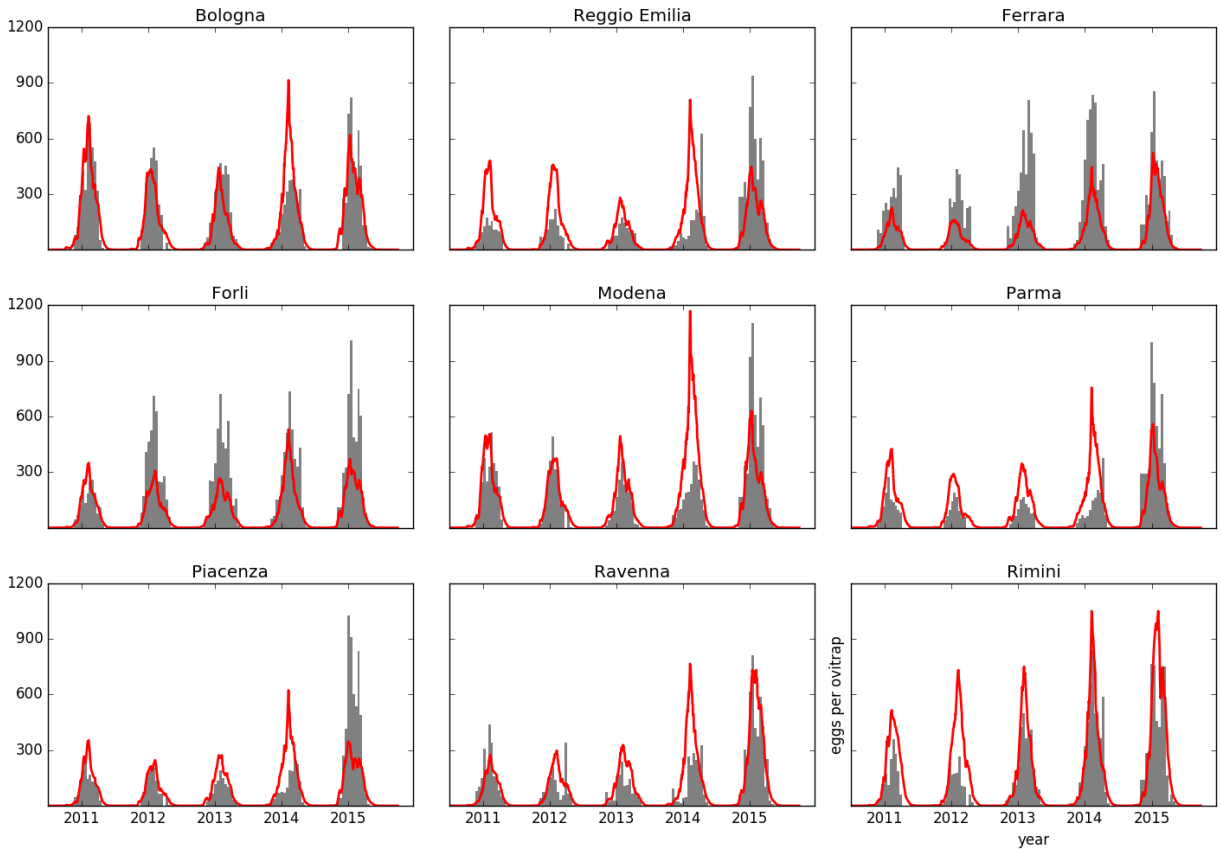

Figure 2.7: Temporal validation. Grey bars show observed *Ae. albopictus* container index data from nine regions in northern Italy. The red line indicates model output for laid mosquito eggs (divided by 6.3e4 for scale). The ERG5 Eraclito climate data set has been used to drive the model for 2010 – 2015 to give a one year spin-up.

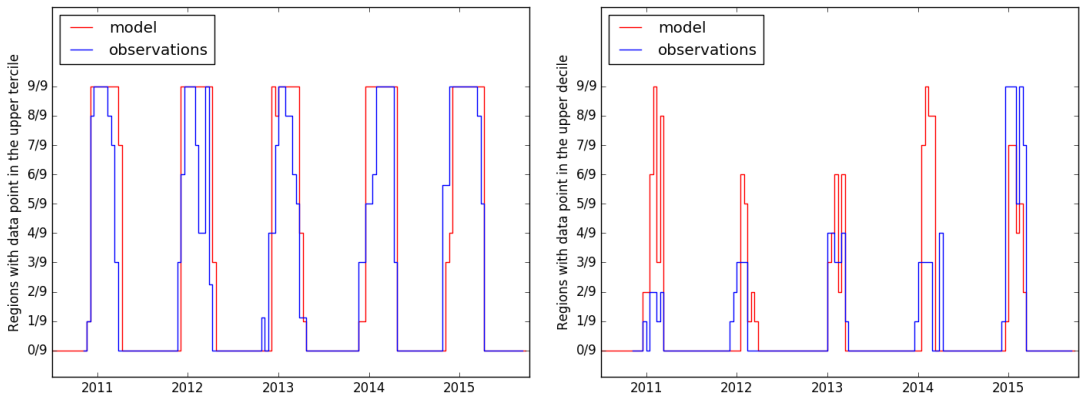

Figure 2.8: CI comparison Comparing the upper tercile (left) and upper decile (right) between observed container index data and simulated egg data. If values of all nine regions lie in the upper tercile/decile of all data points for a specific date, the graph shows a value of 9/9.

effect is then calculated by:

$$\mathrm{EE} = \frac{Y(X_{\mathrm{varied}}) - Y(X_{\mathrm{standard}})}{X_{\mathrm{varied}} - X_{\mathrm{standard}}}$$

with X_{standard} being the standard parameter set as described in Table 2.1, and X_{varied} the parameter set with one (or more) varying parameters. This process is repeated for a number of rounds r. The mean and standard variation of elementary effects are then defined as

$$\mu(\text{EE}) = \frac{1}{r}\sum_{r} \text{EE}_i$$

$$\sigma(\text{EE}) = \sqrt{\frac{1}{r-1}\sum_{r}(\text{EE}_i - \mu)^2}.$$

Comparing the means μ against each other shows which parameter has the biggest influence on the output. Non-linear effects are given by the standard deviation σ. Here, the models sensitivity changes across parameter space, indicating that the parameter in focus interacts with other parameters. Latin Hypercube Sampling is used to vary parameters (uniformly) in the range of $\pm 10\%$ of the standard setting (McKay et al., 2000). The model is then run with the Italian climate data until convergence and the total egg number after five years is taken as reference. *Octave* scripts for these methods come from the SAFE toolbox (Pianosi et al., 2015).

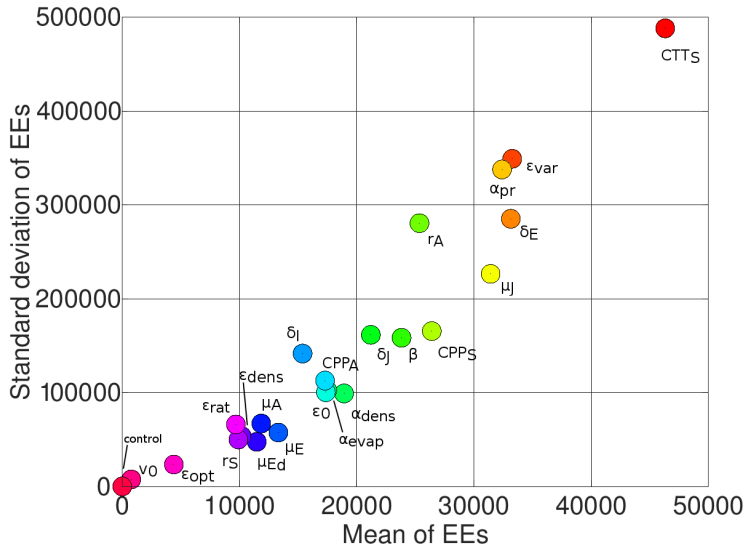

Figure 2.9: Elementary effects test The higher the mean EEs, the more influential the parameter on the model outcome, E_0. The higher the standard deviation of the EEs, the larger its degree of interactions with other parameters.

Figure 2.9 shows that the critical temperature threshold in spring, CTT_S, has the biggest effect on E_0, followed by parameters determining rainfall-dependencies such as ϵ_{var} and α_{rain}, and egg development, δ_E. Other mosquito specific parameters range in the middle. Parameters such as initial egg numbers, v_0, or other hatching rate parameters, ϵ_{dens}, ϵ_{rat} and ϵ_{opt}, have a limited impact on the model output for the Italian climate settings. The distributions for mean and standard deviation of EEs indicate that parameters with a bigger effect on other parameters have a bigger effect on the model output, E_0.

2.3 Results

2.3.1 Diurnal Temperature Range

Including the DTR in simulations affects various parameters involved in population growth. One of the key parameters is the development rate of juveniles, $\delta_J(T)$. This development rate is non-linear, with a maximum at around 30 °C, compare $1/\delta_J$ in Figure A2.1. Looking at temperatures fluctuating around a T_{mean}, we see that if T_{mean} is high, e.g. 30 °C, then any divergence from this optimal development temperature only decreases the rate. If T_{mean} is rather low, however, then 8 °C above T_{mean} have a big positive effect, while 8 °C below T_{mean} only have a slightly negative effect on the development rate. As a result, the integration of the DTR in simulations can have positive or negative effects on population growth, depending on T_{mean}. Figure 2.10 shows the development of egg numbers over 365 days at constant and varying temperatures.

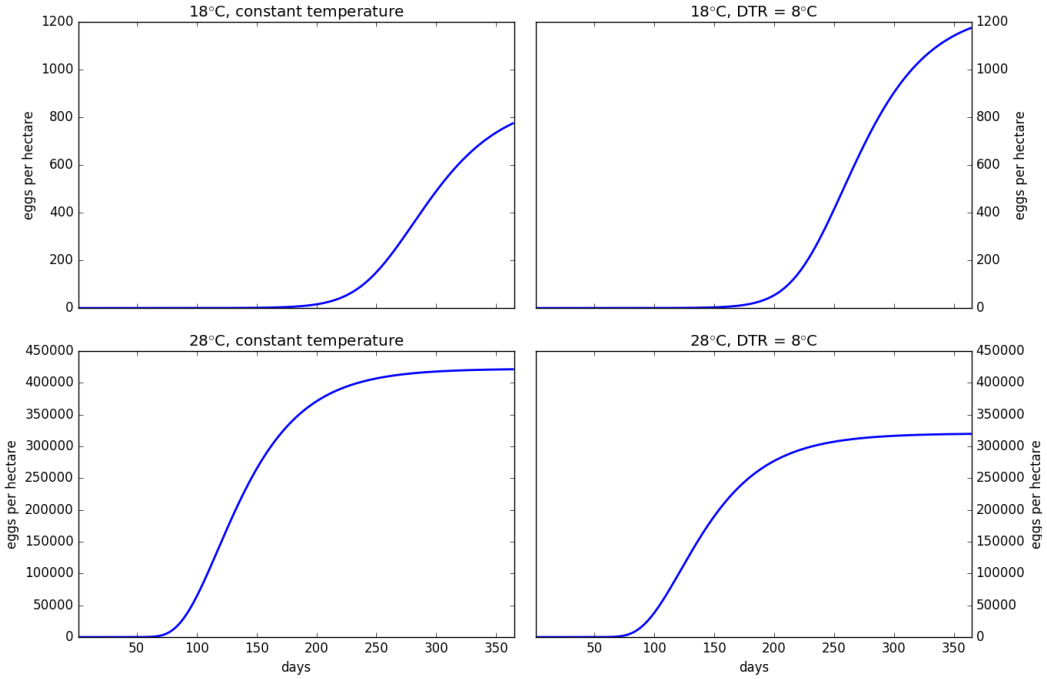

Figure 2.10: DTR impact over time Comparing the development of egg numbers over 365 days at constant 18 °C (top) and 28 °C (bottom) with and without a DTR of 8 °C. The DTR has a positive effect at low temperatures and a negative effect at higher temperatures.

To analyse the effect of the DTR on mosquito population size over a range of mean temperatures, we first run the model under constant conditions (5 mm rainfall per day, 12 hours daylight, 100 humans per km^2, starting with 1 egg per hectare). The model is run with constant mean temperatures (DTR = 0 °C) and afterwards with oscillating temperatures (0 °C < DTR ≤ 12 °C), simulating the diurnal temperature cycle. We then compare absolute mosquito numbers after 365 days by dividing egg numbers that experienced DTR by egg numbers at constant temperatures. We divide for example $E_{18\,°C,DTR=8}(x = 365)$ by $E_{18\,°C,DTR=0}(x = 365)$ from Figure 2.10 to indicate relative population growth at T_{mean} = 18 °C and DTR=8 °C. [2]

[2]The fact that the population size has reached the carrying capacity at 28 °C after 365 days but not quite at

Figure 2.11 shows that oscillating temperatures have a positive effect on the population size at lower mean temperatures, roughly for $14\,°C < T_{\text{mean}} < 24\,°C$. This is actually the lower bound of the mosquito's suitable temperature niche, equilibria and stability analyses show that mosquito populations could survive at constant temperatures between approx. 13 °C and 32 °C, see appendix A2.6. Only when temperatures are very low ($T < 13\,°C$), DTR has a negative effect on the population numbers as mosquitoes experience high mortalities at the reached minimum temperatures.

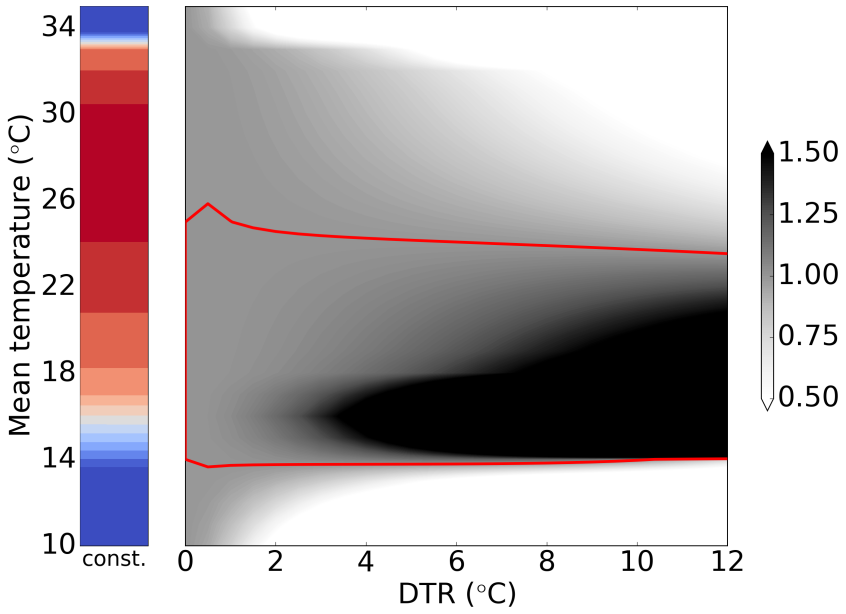

Figure 2.11: DTR impact on mosquito numbers Left panel: Population size of *Ae. albopictus* measured in E_0 at constant temperature, with colour coding as in Figure 2.4. Right panel: Relative population size after 365 days with diurnal temperature cycle compared to the population size experiencing constant temperatures (left panel). Values above 1 (within the red contour line) indicate where oscillating temperatures increase the population size. Mean temperature is given on the y-axis and the DTR is given on the x-axis.

Note that a typical (southern) English summer would be about 17 °C on average, with a DTR of about 10 °C. For these conditions, the DTR has the biggest positive effect on the model outcome, see Figure A2.9, and not using it would therefore lead to an underestimation of actual mosquito numbers.

Running the model with and without DTR also enables us to compare the suitability outputs. Figure 2.12 shows that the northern European regions (England, northern France, Germany, Czech Republic, Scandinavia) show an increased suitability in the model runs that consider the effect of DTR. Spain and the regions around Israel show decreased suitability, while the

18 °C only has a small quantitative but not qualitative effect on the relative population growth.

Balkan region is indifferent. The E-OBS rainfall data set is incomplete for northern Italy and north-east Africa in many years, so the high values in these regions might be not reliable.

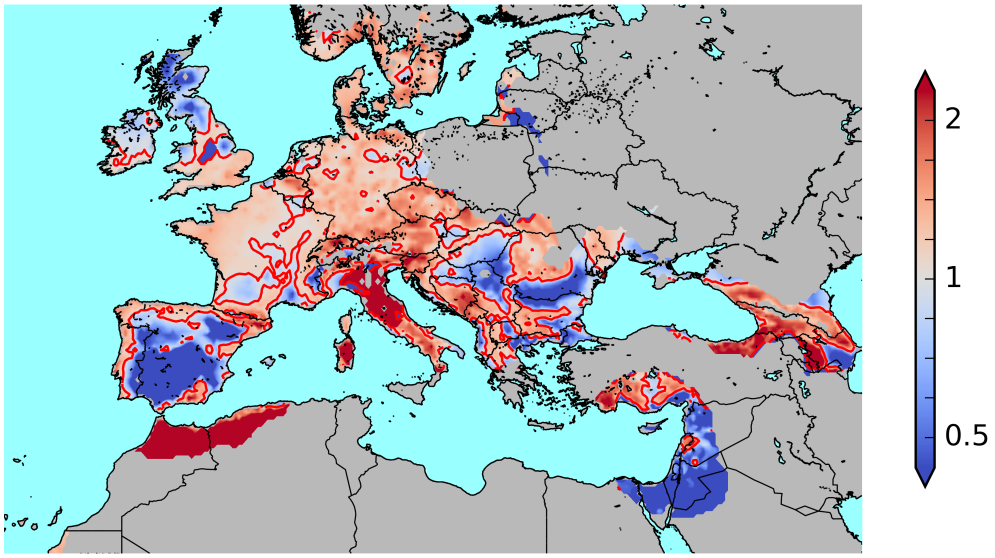

Figure 2.12: DTR impact on simulations Suitability of the DTR run for 2006 – 2016, relative to the run using only daily mean temperatures. The red contour line indicates a value of 1, above which the DTR runs gives more suitable results, and below which the mean temperature runs do.

2.3.2 Current Suitability of the UK

To analyse the UK's suitability for this mosquito, we run our model with two climate data sets for the recent period 2006 – 2016. Figure 2.13 shows how the long-term suitability index E_0 is composed of annual indices E_i, that can be more (2006, 2013, 2014, 2016), or less suitable (2011, 2012).

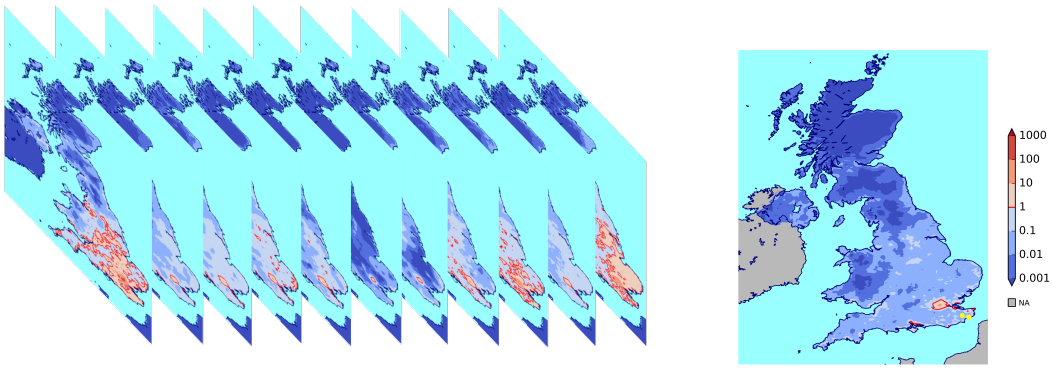

Figure 2.13: Suitability index calculation Running the model for the individual years 2006 until 2016 (left), and taking the geometric mean of the suitability indices E_i gives the final suitability index E_0 (right) for the 10 year period. Climate data: UKCP09.

Figure 2.14 shows that simulations driven by climate data sets with high and low spatial resolution agree in that the London area, the Thames estuary and parts of the southern coast are

already suitable for the mosquito. Other warmer areas around the Severn estuary or in East Anglia, as well as populated northern regions such as Merseyside or around Sheffield are close to but not yet suitable. The Scottish Highlands, the Pennines and the Welsh mountains are unsuitable. Note that we are looking at a 10-year period to analyse the suitability for long-term establishment. We can also look at individual years, finding for example that 2016 was suitable over a larger region of the UK, see Figures 2.5 and 2.13.

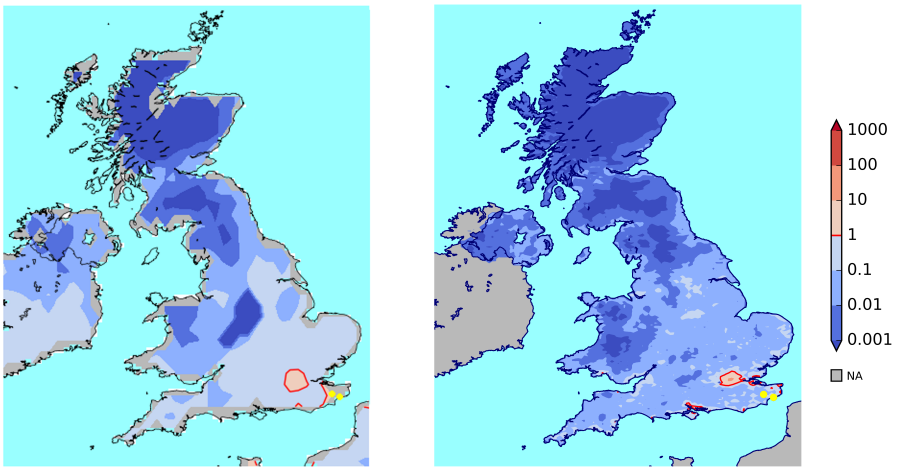

Figure 2.14: UK's suitability for *Ae. albopictus* Comparison of UK mosquito suitability at different spatial resolutions for the years 2006 until 2016, using E-OBS (left) and UKCP09 (right) climate data. Yellow dots show locations where *Ae. albopictus* has been found in 2016 and 2017.

2.3.3 Future Suitability of the UK

Figure 2.15 shows the UK's future mosquito suitability for two emission scenarios, RCP4.5 and RCP8.5, for the 2060s.

Compared with recent UK suitability (Figure 2.14), most of England will have become suitable for the establishment of *Ae. albopictus* populations in about 50 years when looking at the means. Parts of Wales might become suitable, depending on the emission scenario. Scotland and Northern Ireland remain mostly unaffected. However, there are large differences across the five climate models: only the south-east tip of the UK will become suitable with the coldest climate model, while almost the whole UK will become suitable with the warmest model.

Focusing on changes in seasonal abundance, simulations indicate that in current London, *Ae. albopictus* population sizes would be small in early summer and reach relative high number in July and August, see Figure 2.16. Future scenarios show an expansion of this peak into September and an overall increase in numbers. However, the length of the peak mosquito season would be short and population sizes remain low with respect to simulated values in Rome for recent climate conditions. Simulations for Figure 2.16 were started one year ahead of the analysed period and mosquito numbers transferred from the end of a year into the next.

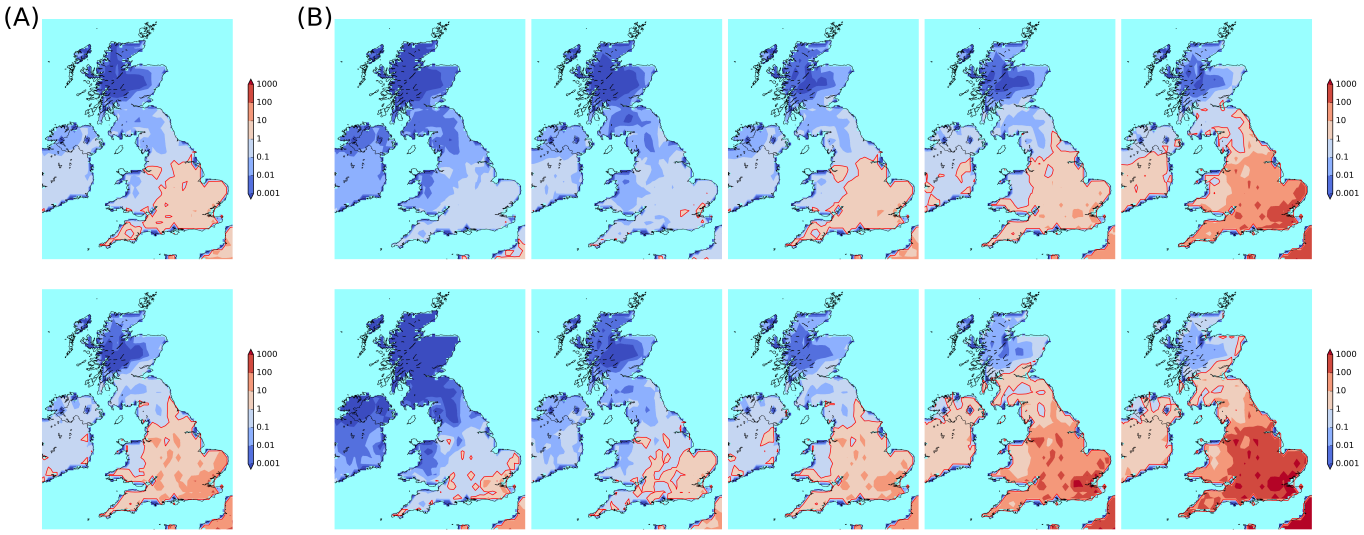

Figure 2.15: UK's future suitability for *Ae. albopictus* Suitability index for 2060–2069. **(A)** Geometric mean over all five model outputs for RCP4.5 (top) and RCP8.5 (bottom). **(B)** Suitability index shown for each climate model individually for RCP4.5 (top) and RCP8.5 (bottom). Left to right: Minimum, 25^{th} quantile, median, 75^{th} quantile, maximum temperature increase for the British Isles. Climate models in order from the coldest to warmest are inmcm4, MRI-CGCM3, NorESM1-M, CanESM2, MIROC-ESM-CHEM for RCP4.5, and inmcm4, CESM1-BGC, NorESM1-M, CanESM2, MIROC-ESM-CHEM for RCP8.5.

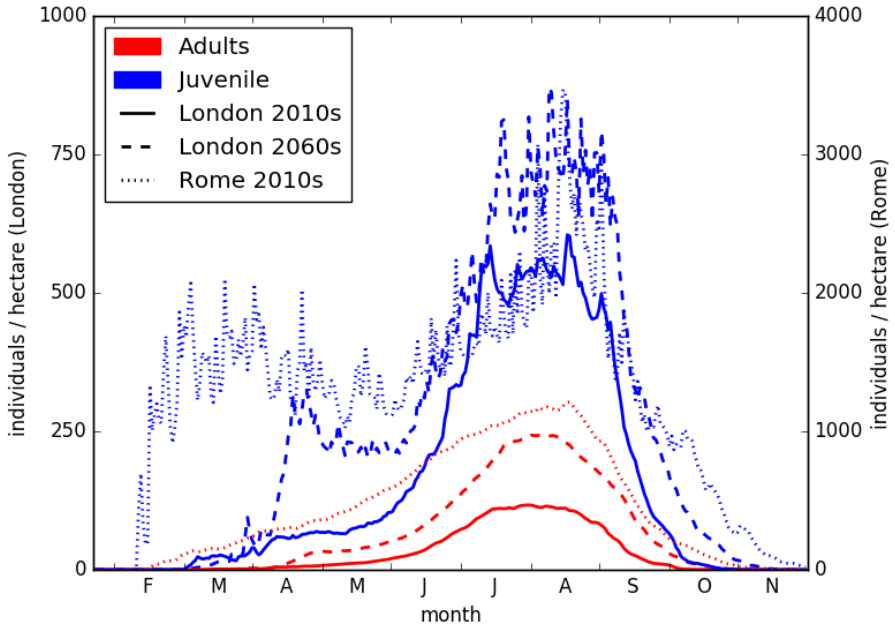

Figure 2.16: Mosquito population dynamics Comparing the simulated length of the mosquito season in London in the 2010s and 2060s and with Rome in the 2010s. Means of 10 years for London and Rome 2010s data, based on E-OBS climate data. Future estimates are based on the ensemble mean of five RCP4.5 projection runs for 2060s. Note the different y-axis for London and Rome.

2.4 Discussion

Numerous studies investigating the climatic dependencies of *Ae. albopictus* have been published in recent years (Thomas et al., 2012; Urbanski et al., 2012; Brady et al., 2013; Lacour et al., 2014, 2015; Rozilawati et al., 2016; Kreß et al., 2017). Taking these new findings into account and building on other modelling studies (Erickson et al., 2010; Jia et al., 2016; Erguler et al., 2016), we developed a dynamical model for *Ae. albopictus* that explicitly simulates the effects of rainfall for egg hatching and larval development, photoperiod for diapause induction and ending, and considers minimum and maximum temperatures that shape mortality and development rates of aquatic and adult stages.

The full temperature range experienced by mosquitoes in the field tend to increase model development rates throughout all stages. Mosquito populations at the lower temperature range (14 °C to 24 °C) develop better with oscillating temperatures. Here, night-time temperatures do not affect the development rates that are quite low anyway, while higher temperatures during the day significantly increase them (Beck-Johnson et al., 2017). Conversely, when mean temperatures are already high, lower night-time temperatures decrease development rates, while even higher temperatures during the day tend to increase mortality rather than development rates (Carrington et al., 2013). Thus, the DTR can be crucial for suitability analyses and should be considered for modelling the life cycle of mosquitoes and other insects (Blanford et al., 2013; Vasseur et al., 2014; Beck-Johnson et al., 2017), as it has already been done for the modelling of temperature-dependent viruses or malaria protozoans that mosquitoes can transmit (Paaijmans et al., 2010; Lambrechts et al., 2011; Wang et al., 2016).

Looking at the UK climate conditions for the past 10 years, we find large parts of the UK rather unsuitable for *Ae. albopictus*, except for some warmer and densely populated areas in the south-east of England. This finding suggests the mosquito has to be introduced into specific areas to enable a long-term establishment. This result differs from findings by other modelling studies showing a medium to high suitability (Fischer et al., 2011; Caminade et al., 2012; ECDC, 2012; Erguler et al., 2016) of larger parts of England with up to five months adult mosquito activity in certain areas (Medlock et al., 2006).

Our results are a bit more conservative because we included rainfall-dependent mechanisms for egg hatching and larval mortalities in the model. Instead of constant egg hatching, we assumed that rainfall events lead to eggs being submerged under water and subsequent hatching. Similar to the finding of Tran et al. (2013), the introduction of a rainfall-dependent egg hatching rate does not improve the model output fit to empirical abundance or ovitrap data. However, we found it enhances model performance in arid and unpopulated areas such as central Spain and Turkey.

We further assumed that a high human population density positively influences both the hatching of eggs and the survival of larvae because the mosquito is able to develop indoors (Dieng et al., 2010), but also in arid but densely populated areas, where water storage and sprinkling

create breeding habitats (Benedict et al., 2007).

While large parts of England might not yet be suitable for a long-term establishment of this mosquito, individual years (especially the warmer recent ones, including 2016) already show a higher suitability which will continue to increase in the future (Liu-Helmersson et al., 2016). Looking 50 years ahead, our projections suggest that *Ae. albopictus*, if introduced, could establish itself over most of England and southern Wales by the 2060s. The mosquito could become abundant in London during future summers; but even severe warming scenarios suggest that population sizes would still remain small with respect to current conditions in Rome, Italy. Large uncertainties indicated by the selected climate models and the emission scenarios are related to the large variability of rainfall and temperature projections in the multi-model ensemble.

The question whether *Ae. albopictus* is able to spread from continental Europe to England is of great importance for public health and veterinary services. This mosquito is a vector that can transmit pathogens that are present or constantly introduced into the UK, including several arboviruses like Zika, dengue and chikungunya (Gould et al., 2006) or the canine heartworm *Dirofilaria immitis* (Genchi et al., 2014). Moreover, it is a very competitive species that could replace endemic mosquito species and become a biting nuisance to the local population (Juliano and Lounibos, 2005; Aranda et al., 2006). Finding parts of south-east England already suitable and predicting a strong increase in suitability for most of England in the future, we highly recommend stringent vector surveillance in southern UK ports and high importation risk areas along motorways (Vaux and Medlock, 2015; Roche et al., 2015). In addition, human and veterinary health services should get prepared to deal with pathogens transmitted by *Ae. albopictus* in warm summers (PHE, 2018), as has recently happened in southern European countries.

Chapter 3

The Spread of *Ae. albopictus* in Europe

The Asian tiger mosquito *Ae. albopictus* is continuously expanding its range in Western Europe. Being introduced to Albania in the 1970s and to Italy in 1990, its covered area is now spanning from southern Spain to central Germany. While the mosquito itself does not fly for long distances, its eggs and adult stages are frequently transported to new environments in vehicles. This man-made diffusion resembles a diffusion process. With this short study we show that the short-distance spread of *Ae. albopictus* in Europe can be modelled mathematically. We use a reaction-diffusion model to describe the mosquito's spread and use recorded occurrence data to evaluate the model output. Findings suggest that *Ae. albopictus* can spread about 100 km per year in southern Europe. We finally apply the findings to the UK, where eggs of this species have already been found. By simulating its possible diffusion in future climates we find that if an introduction in the UK went unnoticed, the mosquito could spread over SE England within 30 years.

3.1 Introduction

The mosquito species *Aedes albopictus* is one of the top invasive species and has spread to all continents except Antarctica (Benedict et al., 2007; Kraemer et al., 2016). Its invasive success is determined by its ecological plasticity that enables it to establish in regions far more temperate than its (sub-)tropical origin (Paupy et al., 2009), as well as global warming through which temperate climate zones become more suitable for this species (Caminade et al., 2012).

The long-distance spread of *Ae. albopictus* is driven by transportation of desiccation-resistant eggs on used tyres or lucky bamboo pot plants (Vaux and Medlock, 2015). But while these mechanisms can bridge large distances in geographically distant regions, enabling the mosquito to reach foreign countries and continents (Sherpa et al., 2019), the short-distance spread of this species seems to follow another pattern. Studies suggest that a key driver of the short-distance spread of *Ae. albopictus* are adult female mosquitoes trapped in cars or lorries and carried around (Roche et al., 2015; Eritja et al., 2017). Either already gestating or finding a blood meal during the transport, the trapped female can then lay its eggs where it is released from the car, especially along highway resting sites or in cities (Roche et al., 2015; Medlock et al., 2017).

The jump of invasive species from continent to continent is stochastic and hard to predict (Jerde and Lewis, 2007; Keller et al., 2011). In contrast, the spread in continuous areas can be modelled with biological invasion models (Holmes et al., 1994). One of the first using these invasion models was Skellam (1951), showing how the spread of plants, invertebrates and mammals can be described with mathematical models, or more precisely with so called reaction-diffusion equations. These equations consist of a diffusion term, describing the spread of individuals, and a reaction term, often describing population reproduction processes or other interactions. Kareiva (1983) used the same diffusion approach to analyse the dispersal of different insect species, later adding predator-prey interactions as reaction terms to the model (Kareiva and Odell, 1987). Besides reaction and diffusion terms, other components such as advection terms to describe e.g. directed transport by wind can by added too (Takahashi et al., 2005).

More recently, the spread of *Aedes* mosquitoes has been modelled. Studies investigate mitigation measures such as insecticides and sterile male releases (Dufourd and Dumont, 2013; Yamashita et al., 2018), local mosquito dispersal in cities (Takahashi et al., 2005) or regional dispersal in Germany (He and Richter, 2018), or the spread of dengue by *Ae. aegypti* (Maidana and Yang, 2008).

Here, we analyse the spread of *Ae. albopictus* in Europe since its introduction to Genoa in 1990. The model system is based on the the model of chapter 2, with modifications to describe the short-distance spread of mosquito eggs or adult females by human transport. We evaluate the model with mosquito occurrence data and use travelling waves to analyse the spread in Europe in one and two dimensions, before we finally simulate an introduction of *Ae. albopictus* in SE England, with subsequent spread in the UK for the next 30 years.

3.2 Model & Methods

3.2.1 Diffusion Model

To model the spread of *Ae. albopictus* in Europe, we decided to extend the ODE model from chapter 2 with a diffusion process of adult female mosquitoes. Diffusing the mature mosquito stage directly accounts for gestating females that get trapped in cars, get carried around and subsequently lay their eggs in a new location. It indirectly also accounts for eggs that are for example laid in used tyres which then get carried around to new locations.

The resulting partial differential equations (PDEs) with a simple diffusion process are given by:

$$\begin{aligned}
\partial_t E(x,t) &= \beta\,(1-\omega)\,A(x,t) - h\,\delta_\mathrm{E}\,E(x,t) - \mu_\mathrm{E}\,E(x,t)\\
\partial_t J(x,t) &= h\,\delta_\mathrm{E}\,E(x,t) + h\,\sigma\,\gamma\,E_\mathrm{d}(x,t) - \delta_\mathrm{J}\,J(x,t) - \mu_\mathrm{J}\,J(x,t) - \frac{J(x,t)^2}{K}\\
\partial_t I(x,t) &= \tfrac{1}{2}\,\delta_\mathrm{J}\,J(x,t) - \delta_\mathrm{I}\,I(x,t) - \mu_\mathrm{A}\,I(x,t)\\
\partial_t A(x,t) &= D\Delta A(x,t) + \delta_\mathrm{I}\,I(x,t) - \mu_\mathrm{A}\,A(x,t)\\
\partial_t E_\mathrm{d}(x,t) &= \beta\,\omega\,A(x,t) - h\,\sigma\,E_\mathrm{d}(x,t)
\end{aligned}$$

with D being the diffusion coefficient, and x the location variable either in 1D or $x = (x_1, x_2)$ in 2D.[1] The Laplace operator Δ is a differential operator such that in two dimensional space $\Delta A = \frac{\partial^2 A}{\partial x_1^2} + \frac{\partial^2 A}{\partial x_2^2}$. Note that the rest of the equations are the same as the ODE model given in chapter 2, and we use parameter definitions from section 2.2.1, Table 2.1. The diffusion coefficient D is a measure for the mobility of the mosquitoes. It is thus proportional to the area that gets covered by the mosquitoes after certain time steps. Its radius is given by the root mean squared displacement, RMSD, of all individuals:

$$\mathrm{RMSD} = \sqrt{2\,n\,D\,\tau}$$

with n the spatial dimensions, here $n = 2$, and τ the time step, here $\tau = 1$ day[2]. The RMSD is easier to interpret than the diffusion coefficient and we will often refer to RMSD instead of D. The relation between the RMSD and the diffusion coefficient was originally used by Einstein (1905) to describe particles in Brownian motion. The same rules that describe the random walk of a particle in a fluid apply to the (random) movement of mosquitoes. We assume that the adult females get carried around randomly, thereby neglecting directed traffic and movement between transport hubs. The area that gets covered by the individuals is continuously increasing under constant conditions (Holmes et al., 1994).

To solve this partial differential equation system numerically, we use an IMEX (**IM**plicit-**EX**plicit) method. An implicit method (here backwards Euler) is used for space and an explicit method (here forward Euler) is used for time steps (Rasheed, 2014). See Appendix A3.1 for mathematical details.

[1] Here, $x = (x_1, x_2)$ but, for readability, we will not use the notation of $\mathbf{x}$ or $\vec{x}$ often found in mathematics.
[2] Not to be confused with the step size in time used for the PDE solver, Δt.

3.2.2 Mosquito and Climate Data

Ae. albopictus occurrence data from Kraemer et al. (2016) with approximate year of recording, updated with recent literature (compare section 2.2.1), is used to fit the diffusion coefficient. Figure 3.1 shows the distribution of *Ae. albopictus* in Europe with its three locations of introduction and subsequent spread.

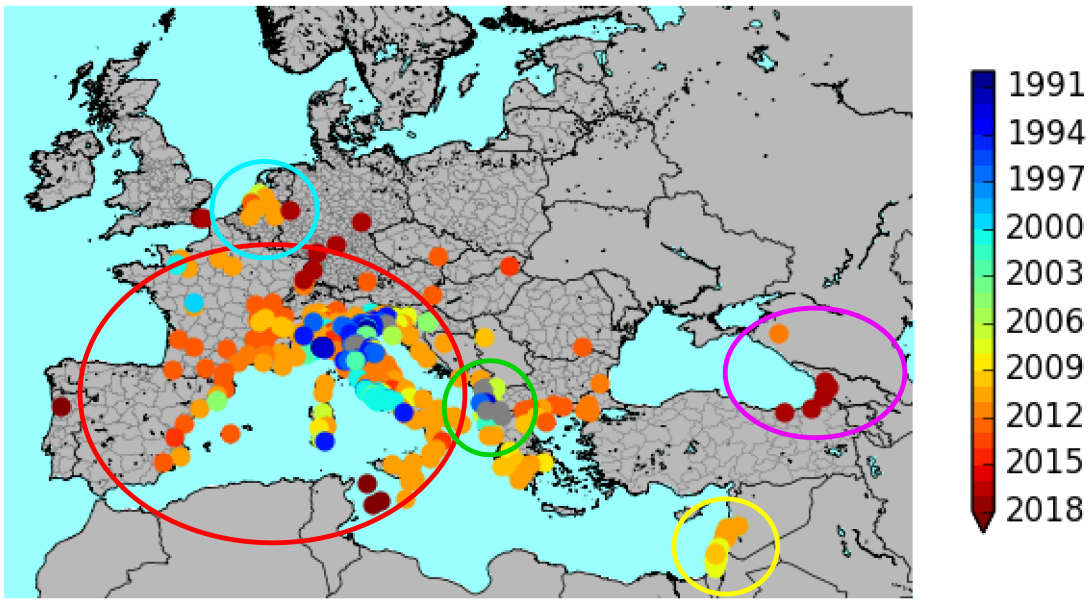

Figure 3.1: Recorded distribution of *Ae. albopictus* This mosquito has been introduced at least three times into Europe: Into Albania in the 1970s (green circle), into Genoa, Italy in 1990 (red circle) and into the Netherlands after 2005 (light blue circle). Other populations exist around the eastern Black Sea (Russia/Georgia/Turkey, purple circle) and the south-eastern shore of the Mediterranean Sea (Israel/Lebanon, yellow circle). Dot colour indicates the year of recording, with grey for missing data.

In this study, we will focus on *Ae. albopictus*' spread since its introduction to Genoa in Northern Italy in 1990 and neglect other introductions to Albania and the Netherlands as the spread especially in Eastern Europe has not been monitored as closely (compare data points in Kraemer et al., 2016).

For the mosquito's population dynamics, we used the E-OBS gridded climate data set on a 25 km × 25 km spatial scale for the period 1990–2017 in Europe (Haylock et al., 2008) and climate projection of the NorESM1-M climate model from the NASA NEX-GDDP project, also on a 25 km × 25 km spatial scale (Thrasher et al., 2012). We chose the NorESM1-M climate model out of all 21 climate models of the NEX-GDDP project because it showed the medium warming for the UK for both emission scenarios RCP4.5 and RCP8.5, see appendix A2.5 and A3.2 for details. Human population density is based on the GPWv4 data set (Doxsey-Whitfield et al., 2015).

Note that precipitation data in the E-OBS data set is incomplete, see Figure 3.2. The diffused class of mature females is independent of rainfall but mosquito reproduction with larval stages

is not. The population dynamics in this region are consequently not accurate after 2007. This affects for example the simulated spread from the north to the south of Italy and would give biased results for this region if the mosquito did not reach southern Italy before 2007. However, we found that this issue does not arise unless D is very small ($D < 0.05 \frac{km^2}{\text{day}}$) and thus does not effect our results.

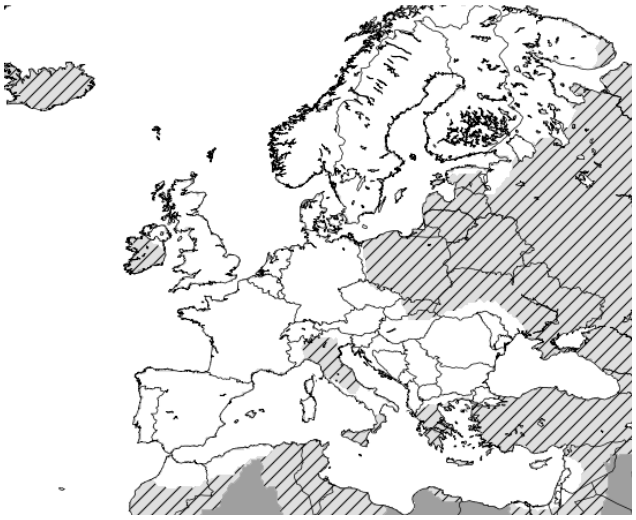

Figure 3.2: E-OBS precipitation data Missing precipitation date in the E-OBS data set. Hatched areas indicate incomplete data since the 1990s, areas in dark grey indicate where data is completely missing since 1990. Data for Northern Italy, for example, is complete from 1990 to 2006, but missing from 1$^{\text{st}}$ January 2007 onwards.

We estimate the threshold of detectable mosquito populations to be 1 egg per hectare at the end of the year.

Metric

To evaluate our model output, we developed a metric M that rewards the simulated establishment of mosquitoes in grid cells that contain an actual recording (i.e. the simulated covered area in year i should contain all recordings to and including year i). At the same time, the metric penalises very large areas of establishment to avoid a spread that is too fast. We thus set the simulated area in which the mosquito has become established, A_c in relation to the occurrence points of year i and previous years that are covered by this area, P_c. In detail, we divide the number of covered occurrence points, P_c, by the number of points that are not covered, $P_{\max} - P_c$, and multiply by a scaled inverse of the covered area:

$$M_i = \frac{P_c}{P_{\max} - P_c} \cdot \frac{A_s}{A_c}$$

with A_s being the scaling factor. Here we chose A_s=15625 km^2 to yield values of M between 0 and 1. Using the mean of the M_i for years i running from 1990 to 2017 gives the final metric $M = \frac{1}{n} \sum_{i=1990}^{2017} M_i$ that is maximised to cover as many occurrence points as possible by keeping the covered area small. We use eggs at the end of the year $E_d(t = 365)$ as an indicator for the covered area.

3.2.3 Travelling Waves

Some reaction-diffusion type model have so called travelling waves as a solution (Murray, 2003). These solutions represent the reproducing individuals spreading outwards from their origin into unoccupied areas in the form of a wave. These waves move with constant speed and shape (Holmes et al., 1994). Travelling waves have important applications in biology and epidemiology; they have been used to analyse resource-consumer dynamics (Gourley, 2000), egg fertilisation processes (Gilkey et al., 1978), and disease propagation in susceptible populations (Murray and Seward, 1992; Abramson et al., 2003).

Here, we use an RMSD of 50 m to show how the mosquito would spread in Europe under constant environmental conditions (year-round temperature of 20 °C and precipitation plus human density such that the carrying capacity is at 10^6 larvae-days per hectare in all areas). Figure 3.3 (left) shows the mosquito spread in 2D, covering the same distance every 5 years. Figure 3.3 (right) shows the spread in 1D, when we slice Europe at latitude 44.5 °N. It can be seen that shape and speed of the travelling waves stay constant throughout the years.

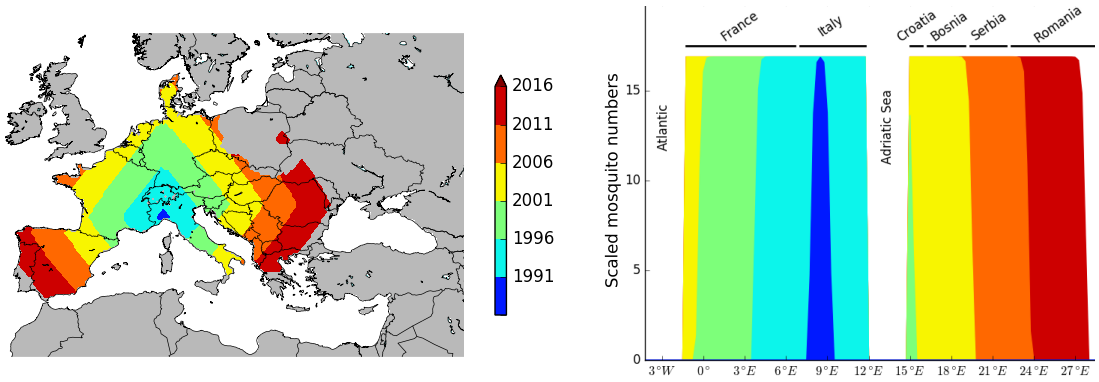

Figure 3.3: Travelling waves under constant environmental conditions Originating in Genoa in 1990, the waves move uniformly in all directions. *Left*: The spread in 2D throughout Europe from 1990 to 2017. *Right*: Waves along latitude 44.5 °N, from the Atlantic in the west to the Black Sea in the east. The waves going east have to "flow" around the Adriatic Sea between 12 and 15 °E and thus arrive a bit later compared to the ones going west.

3.3 Results

3.3.1 Spread in Europe

By using different values for the diffusion coefficient D, we found that a D corresponding to a RMSD of 1500 m gives a good fit to model the spread of *Ae. albopictus* in Europe, see Figure 3.4. Lower D lead to a spread that is too slow, not covering enough occurrence points, while higher D lead to a spread that is too fast, covering too large areas, see Table 3.1. See appendix A3.3 for plots with other RMSD.

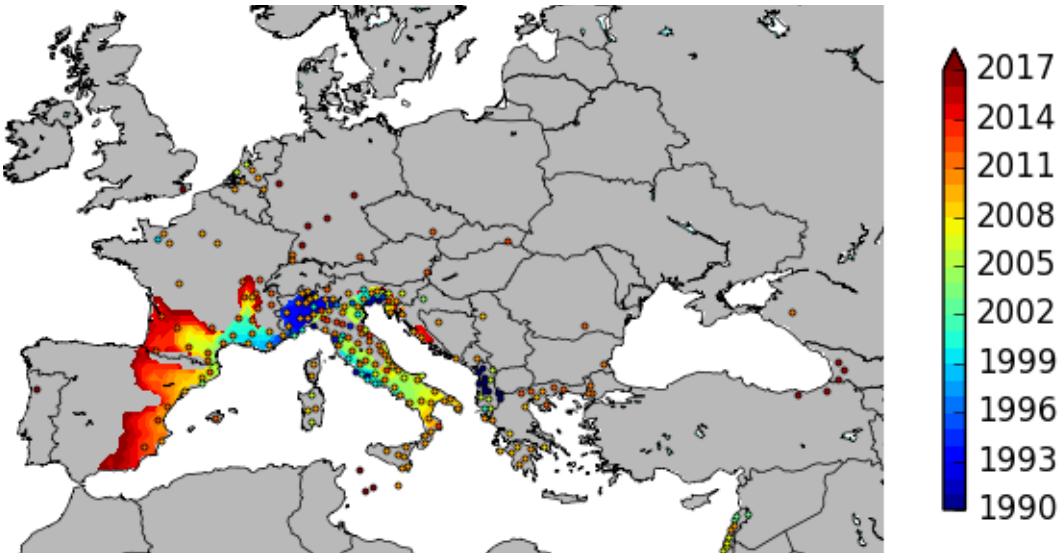

Figure 3.4: Spread in Europe The RMSD was 1500 m. A threshold of 1 egg per hectare has been chosen as detectable cut off. The background colour indicates the year the mosquito could have been observed in the area in our simulation, coloured dots show years and places of actual recordings.

Table 3.1: RMSD Diffusion coefficients D with their corresponding root mean displacements, RMSD, and the goodness of model fit, measured in M.

D	RMSD	M
0.00001 $\frac{625\,km^2}{day}$	158 m	0.397
0.0001 $\frac{625\,km^2}{day}$	500 m	0.397
0.0009 $\frac{625\,km^2}{day}$	1500 m	0.433
0.0025 $\frac{625\,km^2}{day}$	2500 m	0.371
0.01 $\frac{625\,km^2}{day}$	5000 m	0.242

The simulated spread obtained with an RMSD of 1500 m suggests that *Ae. albopictus* had established in the regions Liguria, Piedmont and Lombardy in Northern Italy during the first five years. It then spread along the Italian west coast and the Golf of Venice area by 2000 which perfectly fits with observation data (Romi, 2001). It spread along the French Riviera, before reaching Catalonia in Spain and Southern Italy in 2005, compare Aranda et al. (2006); Bella et al. (2018). It also reaches Parma, separated from Genoa by the Apennines, just in 2005

(Peretti et al., 2009). By 2017, the mosquito has spread further along the coast, spanning the Mediterranean from Gibraltar in the west to Croatia in the east. In France, it has spread along the Rhône valley as far north as Dijon, and along the Atlantic coast up to La Rochelle (Roche et al., 2015; ECDC Vectornet, 2019).

The model misses recent establishments of *Ae. albopictus* in Germany, though. Most likely, this is because not enough mosquitoes get transported across the Alps in vehicles, at least not in high enough numbers to establish a detectable colony in the recent, more suitable years (compare chapter 2). The model also misses some sudden jumps, during which mosquitoes were found in unconnected areas, e.g in Paris (2015), in a range of German cities (2016 - present), or in Portugal (2018) (ECDC Vectornet, 2019; Ministère des Solidarités et de la Santé, 2019).

The mosquitoes can, however, appear in unconnected areas. In this case small numbers get diffused across unsuitable areas and build up numbers in more suitable regions. For example, mosquitoes can establish in the more suitable southern parts of Croatia but not in the northern parts, see Figure 3.4. The cluster of mosquito occurrences in Greece most likely stems from the Albanian population (Sherpa et al., 2019) and is thus not covered by the model.

In addition to a simple diffusion process with a constant diffusion coefficient D, we investigated two other scenarios; one scenario that is looking at an increasing diffusion rate with time as Roche et al. (2015) suggested an accelerated spread in recent years. Another scenario is looking at diffusion rates that are higher in densely populated areas, see appendix A3.4 for details.

Realised Waves

The actual spread of the mosquito under real climatic conditions looks very different to the travelling waves found with constant conditions, see Figure 3.5. Despite using a higher RMSD, the realised "waves" are much slower, due to experienced seasonal changes and lower annual mean temperatures. Note that the climate does not affect the diffusion process, it only affects the population dynamics, resulting in fewer individuals to be spread. The waves' shape is also irregular, due to the difference in (climatic) habitat suitability. Especially mountainous regions are obstacles for the mosquito spread in the simulations, although the mosquito can get carried across mountains more easily in the real world, for example across the Swiss Alps (Flacio et al., 2016), see Figure 3.5. In the east, the waves are brought to a complete stop by the Dinarides, the mountain range at the east coast of the Adriatic Sea. The stronger continental winters on the Balkan will prevent a spread that goes further eastwards too.

Note that the resulting patchiness of the distribution is sometimes modelled with "ecological diffusion" in other invasion models (Garlick et al., 2011). In these models, the individuals do not smoothly distribute to the whole domain after a certain time, but build patches, depending on an irregular diffusion coefficient. This is in contrast to our assumption of Fickian diffusion, in which individuals spread regularly away from a source. The heterogeneous distribution is the result of the reaction terms (heterogeneous habitat suitability), rather than the diffusion

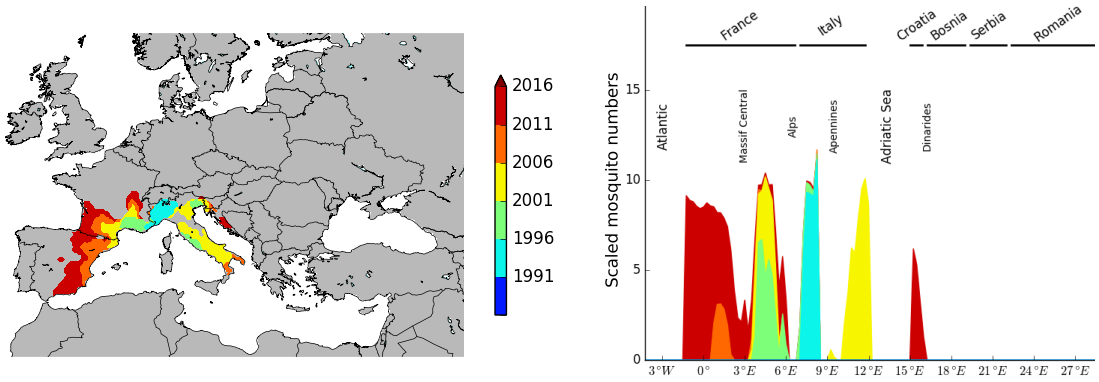

Figure 3.5: Travelling waves under realistic conditions The actual spread with historical climate data (E-OBS, 1990–2017). Left: The spread in Europe, same as in Figure 3.4. Right: The actual spread along latitude 44.5 °N. Mosquito movement is suppressed by mountain ranges, especially east of longitude 17 °E.

process.

3.3.2 Potential Spread in the UK

Ultimately, we run the diffusion model with climate projection data for the UK to simulate the spread of *Ae. albopictus* for the case of an undetected introduction. We introduce 100 normal eggs at the end of August 2019 to Maidstone in Kent, close to where previous eggs of this species had been found (Medlock et al., 2017). For both scenarios, the mosquito will be able to spread across all of SE England, just a bit faster and further for the warmer RCP8.5 scenario, see Figure 3.6.

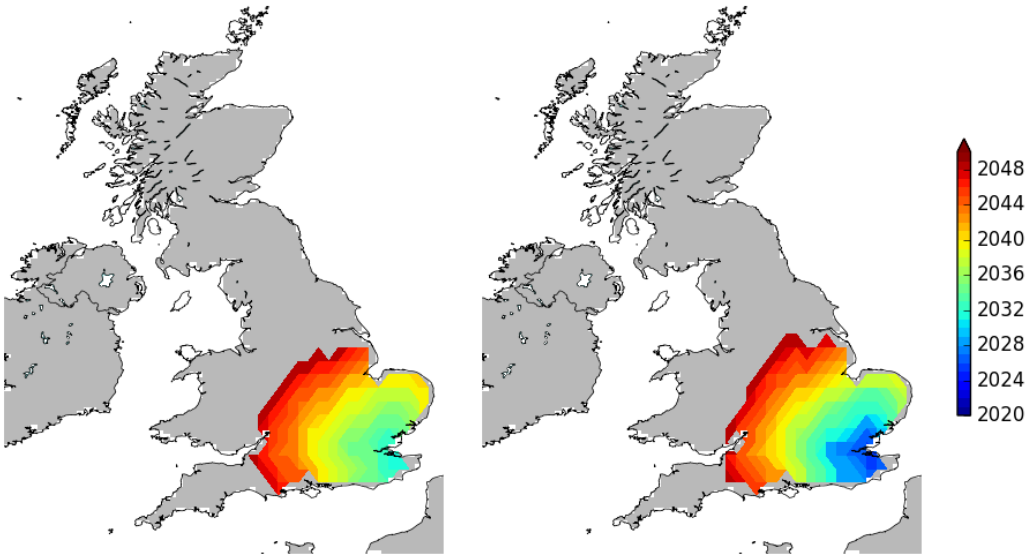

Figure 3.6: Spread in the UK Shown is a projected spread of *Ae. albopictus* in the UK if introduced in summer 2019. Left: RCP4.5. Right: RCP8.5.

In the RCP4.5 scenario, the mosquito would be present in the first ten years but in such small

numbers, that it would not be detected (with a threshold of 1 egg per hectare). In the RCP8.5 scenario, it would become detectable after five years. It should be noted that the absolute spread speed is much lower compared to the spread along the Mediterranean coast; simulations using the same diffusion coefficient suggest that the mosquito could have spread 400 to 500 km per five years in Italy and Spain in the past (compare Figure 3.5), while it would only spread about 80 km in England in the future. However, once established in SE England, the mosquito could probably reach other regions such as Merseyside much faster by long-distance transport.

3.4 Discussion

In this study, we analysed the dispersal of *Ae. albopictus*. We found that reaction-diffusion equations are able to realistically simulate its spread in Western Europe, since it was introduced to northern Italy in 1990. By taking the diffusion rate that was found for Europe and applying it to future UK climates, we found that the mosquito would be able to spread throughout SE England in the next 30 years. Mosquito numbers might be so low in the first five to ten years though, that a single introduction might have a high chance of extinction.

The modelled distribution shows a very good fit with observed occurrences over the years, for example in Italy as of 2000 (Romi, 2001). Results also suggest that while the spread along the Rhône valley in France is probably facilitated by the big motorway A7 (Roche et al., 2015), it was only made possible by the favourable climatic conditions in that area of France (compare also Figure 2.4). In general, we found a spread speed of about 100 km per year for southern Europe, which is very close to the recent work by Kraemer et al. (2019) with different methods. While the total spread by the end of the simulation in 2017 also fits the current distribution of *Ae. albopictus* in Western Europe very well, it misses some points in isolated cities in Germany, while it overpredicts the covered area in Spain. This is probably caused by mispredicted habitat suitability and not affected by the diffusion process, compare chapter 2 with discussion.

Though *Ae. albopictus* is now present over the whole Mediterranean area and further up north, we only focus on Western Europe due to a lack of observation data from Eastern Europe. The mosquito was recorded in 1979 in Albania (Adhami and Reiter, 1998) but no occurrence has been recorded for Eastern Europe in the entire 1980s and 90s (compare data in Kraemer et al., 2016). We thus neglected its presence around the Black Sea and the introduction to Albania for this study. We also neglected the possibility of multiple introductions to Italy (Urbanelli et al., 2000; Manni et al., 2017; Sherpa et al., 2019), probably of strains from the US or/and Japan (Goubert et al., 2016), as it is unclear when and where a second or third introduction might have happened.

In this study, we do not make a difference between mosquito dispersal by mosquito flight or human activity. We do, however, attribute the main part to human activity. *Ae. albopictus* and *Ae. aegypti* only fly about 200 m away from their hatching place in their entire life time (Turell et al., 2005). However, it was shown that for example *Ae. aegypti* is able fly distances of 1000 m in a couple of days (over sea, i.e. without rest and cover possibilities) (Shannon et al., 1930) or 400 m over land (Reiter et al., 1995). A model that analyses inner-city dispersion by mosquito flight has been developed by Takahashi et al. (2005).

Of course, human transport can lead to much larger invasive jumps across countries or even continents. The actual dispersal will constitute of a regional, diffusion-driven, part and a long distance dispersal with sudden jumps (Shigesada et al., 1995). A combination of a simple diffusion and a network model (for example with cities as nodes and motorways as edges, or with a human connectivity network) could simulate the spread more accurately. The agent-based

model by Reiner et al. (2014) is a small-scale example of this jumping mechanism. In their study, they modelled the spread of dengue by human movement in a city with connected houses as nodes.

Looking at the next 30 years, we find that *Ae. albopictus* could successfully spread in the UK following an introduction in a suitable region. The mosquito might even spread without being noticed in the first couple of years, as numbers will be very small. This highlights the importance of PHE surveillance (Vaux and Medlock, 2015) to prevent the establishment and spread of this vector species in the UK.

Chapter 4

A DDE model to assess dengue transmission risk in China

Dengue is considered non-endemic to China. However, travellers frequently import the virus from overseas and local mosquito species spread the disease in the population. As a consequence, China still experiences large outbreaks of dengue. Environmental temperatures play a key role in these outbreaks as they drive development and survival of both vector and virus. To better understand the temperature's implication in the transmission risk of dengue in China, we developed a delay-differential equation model that explicitly simulates temperature-dependent development periods. We analyse mosquito distribution and population dynamic, as well as infection dynamics during the 2014 dengue outbreak in Guangzhou. We show that the outbreak could have lasted for another four weeks if it had not been for mosquito control interventions. Finally, we analyse the China wide dengue transmission risk and compare it to the situation in the UK. We find that southern China, including Guangzhou, can have up to eight month of dengue transmission and even Beijing can have dengue transmission in hot summer months. Looking at the current climate conditions in the UK, we find that London is not warm enough to enable mosquito populations to build up to high numbers and effectively transmit the virus. The results demonstrate the importance of using detailed vector and infection ecology, probably even more so when vector-borne disease transmission is modelled for temperate regions.

4.1 Introduction

Mosquito-borne diseases have always been an issue in China. Arboviruses are numerous (Xia et al., 2017), malaria cases have often reached 20 to 30 million during the last century (Zhou, 1981; Lai et al., 2019) and southern China was a hotspot for filarial nematode transmission (Cano et al., 2014). But while malaria and lymphatic filariasis have been nearly eliminated during this century (WHO, 2010; Lai et al., 2019), arboviruses such as dengue still persist and cause outbreaks with the biggest burden on Yunnan, the province bordering Vietnam, Laos and Myanmar, and Guangdong on the south coast (Xia et al., 2017).

Contrary to other mosquito-borne diseases, dengue cases were only sporadically identified in China in the early 20$^{\text{th}}$ century (Lu et al., 2009). This changed in 1978, when a dengue outbreak with about 22,000 cases occurred in Guangdong province (Wu et al., 2010). Since that year, dengue cases reappear every year, frequently introduced by travellers, leading to local transmission that can result in large dengue outbreaks: about 500,000 cases in 1980, 100,000 cases in 1986 and 50,000 cases in 2014 (Wu et al., 2010; Sun et al., 2017). The city of Guangzhou (aka Canton, 15 million inhabitants, 120 km north of Hong Kong) was the epicentre of the 2014 outbreak that soon spread to the whole province of Guangdong (Zhu et al., 2018). Contrary to a lot of other dengue-ridden regions, the main vector of dengue was not *Ae. aegypti* which is not present anywhere near Guangzhou, but the less efficient vector *Ae. albopictus*, long since established over large parts of China (Jin and Li, 2008).

Numerous studies have investigated the 2014 outbreak, looking for example at the impacts of early year precipitation (Cheng et al., 2016) and resulting surface water for breeding sites (Tian et al., 2016), at the impacts of vaccination and control (Kong et al., 2018), initial case importation and interventions (Cheng et al., 2016, 2017) or human mobility (Zhu et al., 2018, 2019). All of these studies use dynamical models in from of ordinary differential equations, that are useful tools to describe population and infection dynamics (compare chapter 2). However, the description of delayed effects by ODE models is not very accurate. The pathogen incubation period in the mosquito represents such a delayed effect (Wang and Zhao, 2017) and the use of an ODEs can lead to an overestimation of transmission activity. Delayed differential equations (DDEs) can model these effect more accurately.

DDE models have been introduced to entomology by the work by Gurney et al. (1980) on blowflies and by Nisbet and Gurney (1983) on the general theory. Their work was quickly followed by a first DDE model on a mosquito: *Ae. aegypti* (Dye, 1984). DDE models are not as frequently used as ODE models because they are more complex to solve analytically and numerically but a number of studies have been published in more recent years. They have been used for mosquito population dynamics (Ewing et al., 2016; Beck-Johnson et al., 2013) and a range of mosquito-borne disease transmission, including West Nile (Fan et al., 2010), Rift Valley fever (Mweya et al., 2014), chikungunya (Perkins et al., 2015) and malaria (Beck-Johnson et al., 2017).

Here, we develop a new DDE model to simulate mosquito dynamics in China, as well as dengue

transmission dynamics during the 2014 outbreak. We finish by analysing the potential dengue season length for China and apply findings to the UK.

4.2 Model & Methods

4.2.1 Dengue Transmission Model

We use the model developed in chapter 2 as a framework to describe the vector population dynamics. Another class for dengue infected mosquitoes is added to the equation system along with human hosts. In order to describe the infection dynamics more realistically, the transitions between vector classes are modelled using time delays. The resulting delayed differential equation (DDE) model comprises of six equations for the vector and four equations for the human host.

Vector Cycle

The vector cycle is shown in Figure 4.1 and is the same as in chapter 2. Normal eggs E are laid in spring and summer, while diapausing eggs E_d are laid in autumn when days are getting shorter. Normal eggs just hatch after a certain development time, while diapausing eggs overwinter and are activated by warmer temperatures and a longer photoperiod in spring. This is slightly different to the egg activation in chapter 2, which also depended on rainfall (but this would have interfered with the DDE structure of this model). The aquatic juvenile class J develop into newly eclosed male and female adults I. After a resting stage females mature to stage A, take their first blood meal and start to lay eggs.

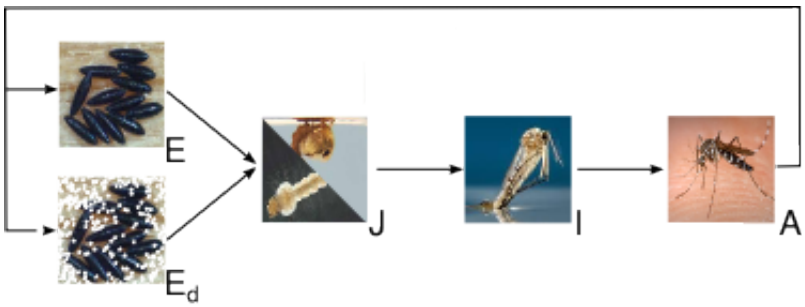

Figure 4.1: DDE model life stages of *Aedes albopictus* The cycle goes from eggs to larvae/pupae (juvenile), to newly eclosed (immature) females, to mature female adults. Adult female mosquitoes lay normal eggs in the summer months or diapausing eggs at the end of the season. Diapausing eggs overwinter and are activated by longer day lengths in spring. Note that this is the same model framework as in chapter 2, Figure 1.

While we used ordinary differential equations in chapter 2, we now use delayed differential equations. The derivation of a DDE model from ODEs is explained in appendix A4.1. The structure of a DDE can be described by a recruitment term R with all incoming individuals from other classes, a maturation term M with the individuals that change to another class, and a mortality term for the individuals that leave the system. With parameter definitions given in Table 4.1 the population dynamics in the vector are described by:

$$
\begin{aligned}
\tfrac{d}{dt}E(t) &= \beta\,(1-\omega)\,A(t) - \beta\,(1-\omega)\,A(t-\tau_E)\,e^{-\int_{t-\tau_E}^{t}\mu_E(\xi)\,d\xi} - \mu_E\,E(t)\\
&= R_E(t) - M_E(t) - \mu_E\,E\\
\tfrac{d}{dt}J(t) &= M_E(t) + \sigma\,\gamma\,E_d(t) - \frac{(M_E(t-\tau_J) + \sigma\,\gamma\,E_d(t-\tau_J))\;e^{-\int_{t-\tau_J}^{t}\mu_J(\xi)\,d\xi}}{1 + (M_E(t-\tau_J) + \sigma\,\gamma\,E_d(t-\tau_J))\int_{t-\tau_J}^{t}L(u)\,du} - \mu_J\,J(t) - \frac{J(t)^2}{K(t)}\\
&= R_J(t) - M_J(t) - \mu_J\,J(t) - \frac{J(t)^2}{K(t)}\\
\tfrac{d}{dt}I(t) &= 0.5\,M_J(t) - 0.5\,M_J(t-\tau_I)\,e^{-\int_{t-\tau_I}^{t}\mu_A(\xi)\,d\xi} - \mu_A\,I(t)\\
&= R_I(t) - M_I(t) - \mu_A\,I(t)\\
\tfrac{d}{dt}A(t) &= M_I(t) - \mu_A\,A(t)\\
\tfrac{d}{dt}E_d(t) &= \beta\,\omega\,A(t) - \sigma\,E_d(t)\\
\text{with } L(u) &= \tfrac{1}{K(u)}\,e^{-\int_{u-\tau_J}^{u}\mu_J(\xi)\,d\xi}.
\end{aligned}
$$

Table 4.1: DDE model parameters Derivation and references of parameters are shown in appendix A2.1. Environmental drivers are temperature, T, rainfall, R, photoperiod, P, latitude, L and human population density, H. This table is nearly identical to the one shown in section 2.2.1, apart from the development times τ that had been rates δ for the ODE model.

	Parameter	**Value/Formula**
$\mathrm{CTT_S}$	Critical temperature in spring (°C)	11.0
$\mathrm{CPP_S}$	Critical photoperiod in spring (hours)	11.25
$\sigma(T,P)$	Spring hatching rate (1/day)	$\begin{cases} 0 & \text{if } T_7 < \mathrm{CTT_S} \text{ or } P < \mathrm{CPP_S} \\ 0.1 & \text{if } T_7 \geq \mathrm{CTT_S} \text{ and } P \geq \mathrm{CPP_S} \end{cases}$
$\mathrm{CPP_A}(L)$	Critical photoperiod in autumn (hours)	$10.058 + 0.08965\,L$
$\omega(P)$	Fraction of eggs going into diapause	$\begin{cases} 0 & \text{if } P > \mathrm{CPP_A} \text{ or } t < 183 \\ 0.5 & \text{if } P \leq \mathrm{CPP_A} \text{ and } t \geq 183 \end{cases}$
τ_E	Normal egg development time (days)	7.1 *
$\tau_\mathrm{J}(T)$	Juvenile development time (days)	$83.85 - 4.89\,T + 0.08\,T^2$
$\tau_\mathrm{I}(T)$	First pre-blood meal time (days)	$50.1 - 3.574\,T + 0.069\,T^2$
$\mu_\mathrm{E}(T)$	Egg mortality rate (1/day)	$-\ln(0.955\,\exp(-0.5\,(\frac{T-18.8}{21.53})^6))$
$\mu_\mathrm{J}(T)$	Juvenile mortality rate (1/day)	$-\ln(0.977\,\exp(-0.5\,(\frac{T-21.8}{16.6})^6))$
$\mu_\mathrm{A}(T_\mathrm{mean})$	Adult mortality rate (1/day)	$-\ln(0.677\,\exp(-0.5\,(\frac{T_\mathrm{mean}-20.9}{13.2})^6)\,T_\mathrm{mean}^{0.1})$
$\gamma(T_\mathrm{DJF,min})$	Survival of diapausing eggs (1/winter)	$0.93\,\exp(-0.5\,(\frac{T_\mathrm{DJF,min}-11.68}{15.67})^6)$
$\beta(T)$	Egg laying rate (1/day)	$\begin{cases} 33.2\,\exp(-0.5\,(\frac{T-70.3}{14.1})^2)\,(38.8-T)^{1.5} & \text{if } T \leq 38.8 \\ 0 & \text{if } T > 38.8 \end{cases}$
λ	Capacity parameter (larvae · days/hectare)	40^4 *

* Estimate for China.

Please note that we do not follow the standard approach for delay differential equation models by Nisbet and Gurney (1983) in which the time delay itself is modelled by a differential equation. Instead, we calculate all time delays before we run the simulations, see appendix A4.2. This is

computationally more intensive but avoids some caveats in delay calculation (compare Erguler et al., 2016).

Disease Dynamics in the Vector

An introduction of dengue into the model leads to one more vector class. We distinguish between susceptible mosquito females, A_S, and infectious females, A_I, see Figure 4.2. When a host seeking female bites an infected human with the biting rate α, it will become exposed with a certain probability b_{HV}. With $\frac{H_I}{N_h}$ as the fraction of infected humans in the local population, this leads to a total infection rate of $\alpha\, b_{HV} \frac{H_I}{N_h}$ for susceptible mosquitoes, A_S. Depending on the temperature-dependent EIP, exposed females will change to the infectious state in which they can infect human hosts. Both susceptible and infected females die with the normal adult mortality, μ_A.

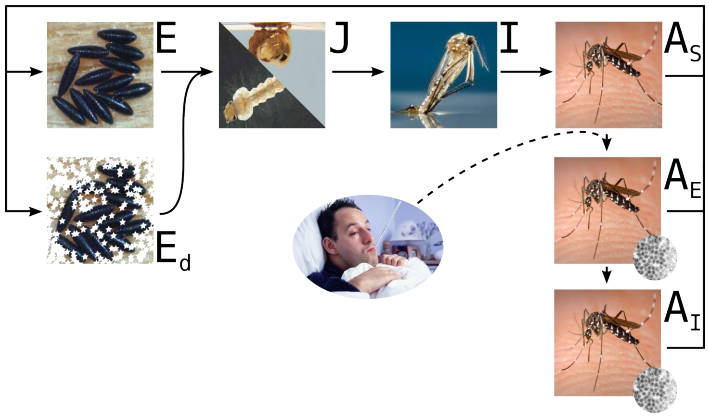

Figure 4.2: DDE model with infections The mosquito life cycle with a sixth class: infectious females. When a susceptible mosquito bites an infected human host, it gets infected with a certain probability (exposed stage) and changes to the infectious class after a temperature-dependent extrinsic incubation period.

The model equation for mature females becomes

$$\frac{d}{dt}A_S(t) = M_I(t) - \alpha\, b_{HV} \frac{H_I(t)}{N_h(t)} A_S(t) - \mu_A\, A_S(t) \tag{4.1}$$

$$\frac{d}{dt}A_E(t) = \alpha\, b_{HV} \frac{H_I(t)}{N_h(t)} A_S(t) - \alpha\, b_{HV} \frac{H_I(t-EIP)}{N_h(t-EIP)} A_S(t-EIP)\, e^{-\int_{t-EIP}^{t} \mu_A(\xi)\, d\xi} - \mu_A\, A_E(t) \tag{4.2}$$

$$\frac{d}{dt}A_I(t) = \alpha\, b_{HV} \frac{H_I(t-EIP)}{N_h(t-EIP)} A_S(t-EIP)\, e^{-\int_{t-EIP}^{t} \mu_A(\xi)\, d\xi} - \mu_A\, A_I(t) \tag{4.3}$$

such that the three adult female classes combined result in the total number of egg-laying females: $A_S + A_E + A_I = A$. Additional parameter definitions are given in Table 4.2. Note that the incidence rate $\alpha\, b_{HV} \frac{H_I}{N_h} A_S$ uses non-delay terms in equation (4.1) but delay terms in equation (4.2). This is explained in more detail in appendix A4.3.

This approach neglects the possibility of vertical virus transmission. In consequence, there is no overwintering of infected eggs that could start a new outbreak in the following year and new

Table 4.2: DDE model parameters Additional parameter definitions and values used for disease dynamics. Derivations of and references related to parameters are the same as in chapter 2 or indicated here.

	Parameter	Value/Formula
α	Biting rate (1/days)	0.05 *
b_{VH}	Infection probability from vector to host	0.5 †
b_{HV}	Infection probability from host to vector	0.31 †
EIP(T)	Extrinsic incubation period (days)	$1.03\,(4 + \exp(5.15 - 0.123\,T))$ ‡
IIP $= \frac{1}{\nu_H}$	Intrinsic incubation period (days)	5 §
r	Recovery rate of humans (1/days)	$\frac{1}{5}$ §

Daily biting rates for *Ae. aegypti* vary between 0.1 and 0.2 blood meals per day (Scott et al., 2000), halved for *Ae. albopictus* (Farjana and Tuno, 2013). † Estimates by Paupy et al. (2010); Manore et al. (2014). ‡ Estimate for *Ae. aegypti* by Liu-Helmersson et al. (2014) with scaling factor for *Ae. albopictus* by Brady et al. (2014). § Estimates by Gubler (1998); WHO (2009).

dengue cases would have to be imported to initiate dengue transmissions.

Disease Dynamics in the Human Host

In contrast to the vector cycle, we model disease dynamics in the human host with ordinary differential equations as they are computationally less expensive to solve (i.e. they do not take as long to run) and the incubation period in the human host is relatively short and temperature-independent.

Human hosts are described by four classes: susceptible H_S, exposed H_E, infected H_I, and recovered H_R. When a susceptible gets bitten by an infected mosquito, it changes to the exposed state by a probability of b_{VH}. It remains in the exposed state for the intrinsic incubation period (IIP) and then changes to the infected state. Infected individuals recover with a rate of r and become immune. We assume that we only have a single dengue serotype circulating in the population. As we look at very small numbers of infections for only short periods, we neglect birth and natural death rates for human hosts as well as (cross-)immunity to serotypes. We also neglect dengue induced mortality as it is usually very low (below 1%) (WHO, 2009) and thus has only marginal effect on disease dynamics. The resulting ODE are given by:

$$\begin{aligned}
\tfrac{d}{dt} H_S &= -\alpha\, b_{VH}\, A_I\, H_S \\
\tfrac{d}{dt} H_E &= \alpha\, b_{VH}\, A_I\, H_S - \nu_H\, H_e \\
\tfrac{d}{dt} H_I &= \nu_H\, H_E - r\, H_I \\
\tfrac{d}{dt} H_R &= r\, H_I
\end{aligned}$$

We do not divide the infection probability term for humans, $\alpha\, b_{VH} A_I H_S$, by the total number of mature mosquitoes, A (density-dependent transmission) while we do divide infection probability term for the vector, $\alpha\, b_{HV} \frac{H_I}{N_h} A_S$ by the total number of humans, N_h in equation (4.3) (frequency-dependent transmission) (Begon et al., 2002). Dividing by the total number of humans accounts for a diluting effect, so that an infected person in a big city is less likely to be bitten than someone in a rural area. This diluting effect does not apply to mosquitoes

equally. The number of newly infected persons depends on the total number rather than on the frequency of infected mosquitoes.

As the DDE model is computationally more expensive to solve, we revert to the ODE model used in chapter 2 to calculate China's suitability for *Ae. albopictus* as it requires the handling of large climate data matrices for a study period of several decades. We also use ODE model runs with infection dynamics (compare appendix A4.3) for comparison with the DDE results.

4.2.2 Mosquito and Dengue Data

We use China wide presence/absence data for *Ae. albopictus* for 2015 to validate our vector suitability predictions. Monthly Breteau index (BI)[1] data were available for 21 out of 34 administrative divisions (provinces/autonomous regions/municipalities) for 2015 to spatially validate population dynamics of the vector. It was also available for Guangzhou for 2006-2015 to validate population dynamics over longer time periods. Dengue data was available for 2010-2015 to validate the modelled infection dynamics.

All data sets were recorded and provided by China CDC. Vector and disease occurrence locations were given on prefecture (300+) or county (2500+) level, and thus had to be pre-processed to allocate mosquito occurrences or disease cases to locations in coordinate format. The geolocation website `http://www.geonames.org/` was used to match the Mandarin characters with a location and retrieve latitude and longitude coordinates. To validate the results, the matching was repeated with a random sample using `http://maps.cga.harvard.edu/` to double check coordinates. The whole process was automated using *Python* scripts.

The 2014 dengue outbreak took place mostly in Guangdong province, with Guangzhou as the epicentre, but also spread to other provinces. To analyse weekly case numbers for only Guangzhou, we included all cases that happened within a 72 km radius around the Guangzhou city centre (23.09 °N, 113.17 °E).

4.2.3 Climate Data

We use two climate data sets: The APHRODITE gridded data set with a 25 km × 25 km resolution for which daily temperature and rainfall data is available for the period of 1950 to 2007 (Yatagai et al., 2012). We also use weather station data from the Chinese Meteorological Data Service Center (CMCD). The station network comprises more than 800 stations with daily temperature and rainfall data available for 2006 to 2016. Missing rainfall data for weather stations in the CMCD data set were estimated by linearly interpolating the rainfall time series data. The missing values did not have a big impact on model results, as filling them with zeros gave very similar results to the interpolation approach.

[1] The Breteau index measures the number of water containers infested with the mosquitoes per 100 estates or houses inspected.

For single locations, we used data point #86 for Jinan (36.36 °N, 117.00 °E) and #760 for Guangzhou (23.13 N, 113.29 E) from the CMCD data set. For London, which we analyse in the end, we use the grid point at 51.5 °N, 0.3 °W from the gridded UKCP09 climate data set.

4.3 Results

Analytical and numerical solutions agree in that the vector population can persist between 16.5 and 32.5 °C, with an optimal temperature of 27 °C, see appendix A4.4. Both temperature range and optimum are in line with statistical analyses on this species' temperature niche (Brady et al., 2013; Santos and Meneses, 2017). Depending on the temperature, the model predicts that the larval population is about 4 to 30 times bigger than the adult population.

We now first use this model's ODE version from chapter 2 to analyse China's suitability for this species before we use the DDE model to analyse mosquito and disease dynamics.

4.3.1 China's Suitability for *Ae. albopictus*

To analyse China's suitability for *Ae. albopictus*, we run the ODE model with the gridded climate data set for the period 2000 to 2007. Figure 4.3 shows presence/absence data from Wu et al. (2011) and collected by China CDC, in comparison with the modelled suitability index.

The modelled suitability is highly consistent with presence/absence data: 92% of data points are predicted correctly. However, the model misses some suitable locations in the Himalayas close to the border with Nepal, and east of Beijing, right to the border with North Korea. In the first case, the spatial scale of the climate data of 25 km × 25 km might be too coarse to indicate suitable mountain valleys whereas the northern regions experience winters with temperatures below -15 °C. This makes overwintering unlikely by model assumptions but microclimates could help *Ae. albopictus* to survive even here.

On the other hand, the model falsely predicts suitable areas in the Taklamakan desert in western China. While the temperatures would be suitable here, the scarce rainfall prohibits mosquito activity. There are, however, oases and the cities Kashgar and Yarkant with more than 100 000 inhabitants, rivers and relatively mild diurnal temperature ranges on the south-western edge of the desert that could enable mosquito breeding with artificial breeding sites.

We also performed a ROC analysis to check whether the suitability index of one egg at the beginning of the year leading to at least one egg at the end of the year is the best threshold for China, see Figure 4.4 and compare section 2.2.2. We found that the rate of correctly predicted suitability could be slightly improved when we defined areas as suitable where one egg leads to at least 400 eggs after 365 days. With this adapted suitability index, the Taklamakan desert would show up as unsuitable. This is different to the result from Europe, where the best threshold was actually one egg after one year, see Figure 2.6. An explanation could be that we did not include rainfall driven egg hatching in the DDE model, which would probably have masked the Taklamakan desert and led to a lower threshold.

To analyse how China's suitability for this mosquito has changed in the last 50 years, we also compared the suitability index of the most current data available (2000 to 2007) to the 30-years baseline of 1960 to 1990. Figure 4.5 shows that most parts of China have become more suitable,

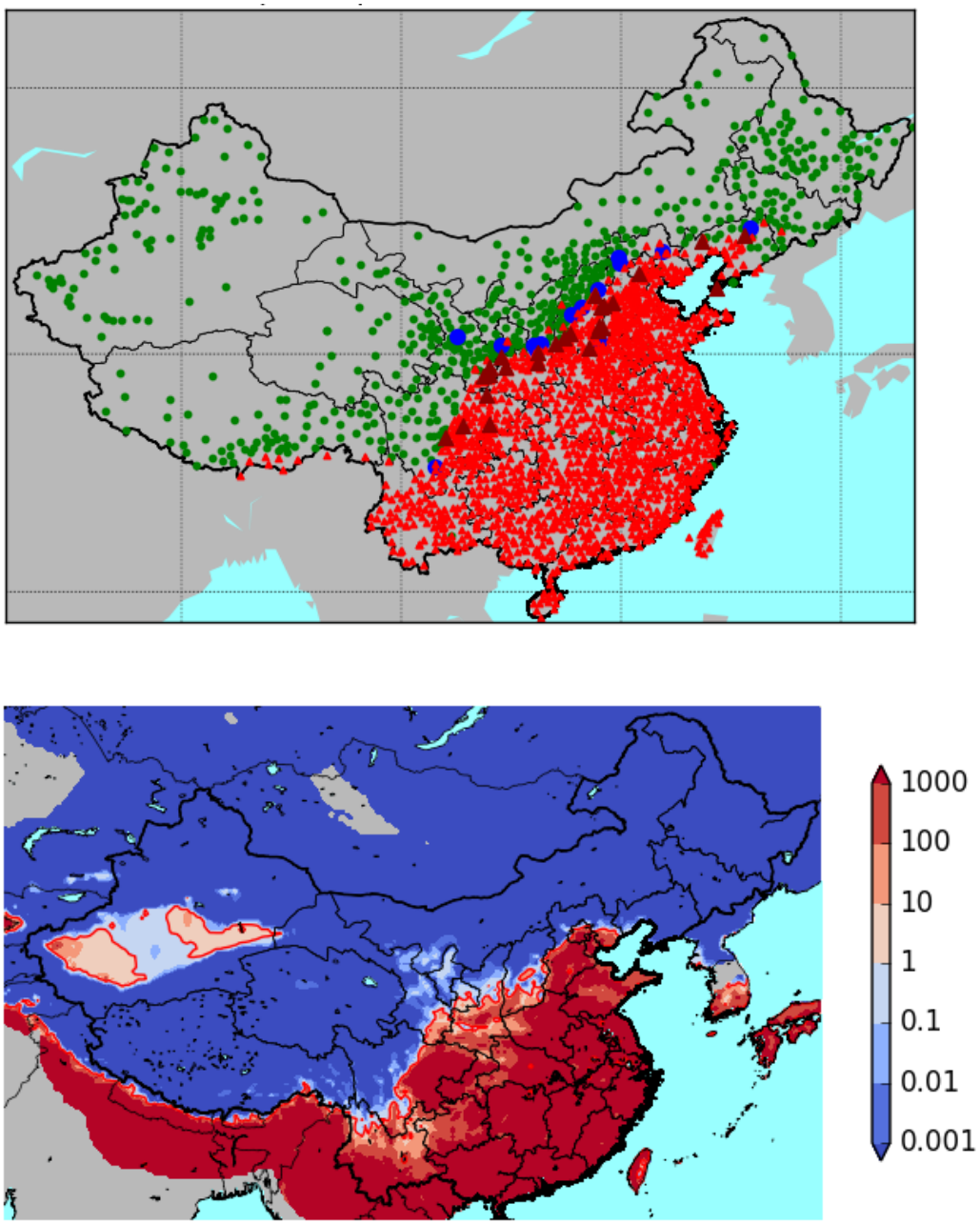

Figure 4.3: China's suitability for *Ae. albopictus* Top: Mosquito presence 2007 (light red) and 2015 (dark red) and absence 2007 (blue) and 2015 (green). Bottom: Modelled suitability index for China without Hainan island for the period 2000 to 2007. The APHRODITE climate data set was used, grey areas indicate incomplete data.

especially in the north-east and in mountainous regions. Only the Tibetan plateau, with annual mean temperatures around 0 °C, seems to be unaffected by this trend.

Breteau Index

In the next step, we checked whether the DDE model could replicate temporal mosquito dynamics and compared model results with Breteau index (BI) data from Guangzhou for 2006 to 2015.

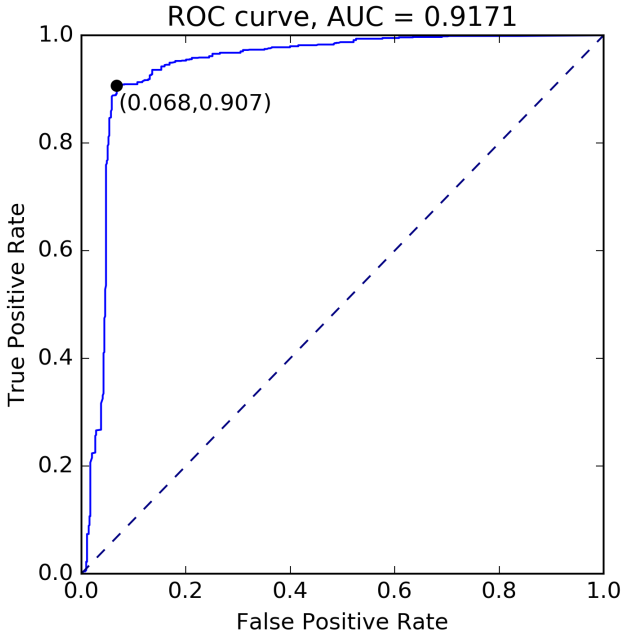

Figure 4.4: ROC for China Receiver operating characteristic curve. The black dot represents Youden's index, the best compromise between specificity (1-FPR) and sensitivity (TPR). The area under the curve (AUC) gives the probability of a region with mosquito occurrence getting a higher suitability index than one without.

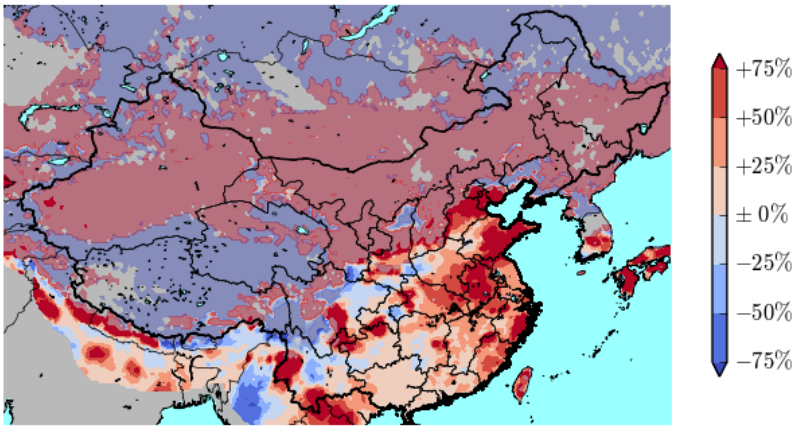

Figure 4.5: China's current suitability (2000-2007) compared to the baseline of 1960-1990. Areas that are not currently suitable (i.e. that do not show up as red in Figure 4.3) are coloured in semi-transparent.

To estimate a BI from mosquito data, we assume that clutches of eggs are randomly (Poisson) distributed to available containers. The probability that a container is positive with one or more egg clutches, multiplied by the number of containers available, gives the BI estimate:

$$BI(t) = b\left(1 - e^{-a\,E(t)}\right). \tag{4.4}$$

$E(t)$ is the number of total eggs in the area at time t, a is a factor to relate total egg num-

bers to egg clutches per water container and b is the mean number of water containers per 100 households. Here, we estimated $a = 0.00001$ and $b = 30$. BI values above 4 can be a good indicator for dengue transmission risk (Sanchez et al., 2006, 2010), however BI often does not correlate with dengue incidence and outbreaks can happen with $BI < 4$ (Bowman et al., 2014), sometimes lagged by up to three months (Sang et al., 2014).

Monthly Breteau indices in Guangzhou were measured at 12 different locations. Two locations (Nansha and Panyu) were situated at the river delta and near a wetland park and showed very high BI values of up to 60 positive containers per 100 houses. Monthly mean model outputs fit the observed BI well (Spearman's $\rho = 0.83$) and correctly indicates years with higher (2008) and lower (2010) numbers than average, see Figure 4.6. 2015, the year after the dengue outbreak with intensive mosquito control measures, saw fewer mosquitoes than expected under normal conditions.

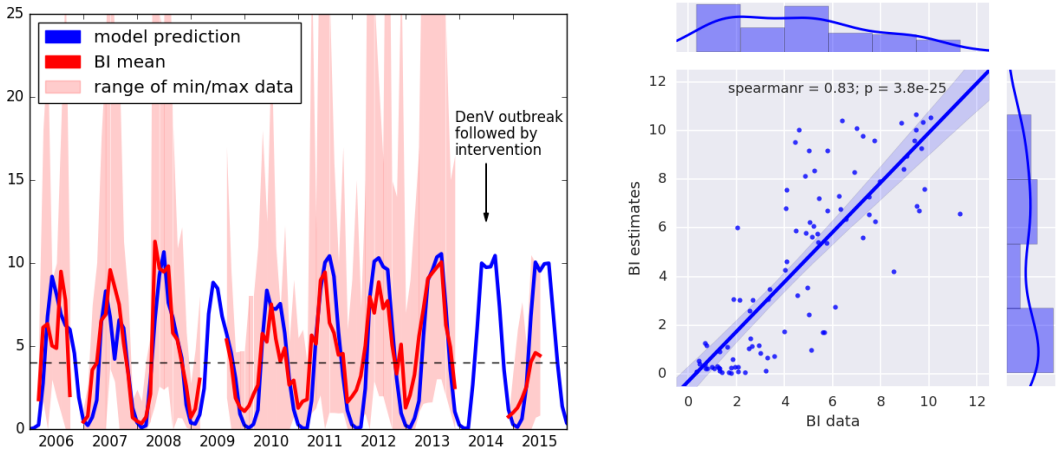

Figure 4.6: Monthly BI data in Guangzhou Left: The modelled Breteau Index in Guangzhou compared to the observed BI. BI values above 4 (dashed line) indicates risk of dengue transmission. Data for 2009 and 2014 were incomplete. Right: Scatter plot of simulated vs. observed BI values. The frequency histograms show that data are not normal distributed and thus the non-parametric Spearman's correlation test has to be used.

Observed BI values in winter are often well above zero and this mosquito activity is not captured by the model. Research by China CDC has shown that larvae can endure temperatures below freezing underneath a sheet of ice for longer time periods. We tried to run model simulations with higher survival at lower temperatures to represent this fact, but it did not increase the fit to BI data. It is also possible that larvae inhabit warmer households in winter and thus survive longer in these microclimates. However, houses in southern China often lack heating systems so that this factor might play less of a role in Guangzhou compared to northern China or Europe. Another study has found lower, but still positive mosquito indices in winter (Xia et al., 2018).

Monthly BI data for 21 out of 34 administrative divisions for the year 2015 allowed to compare model output to spatio-temporal mosquito dynamics. Figure 4.7 shows that the model does okay but does not capture the China wide BI dynamics in 2015 as well as the BI in Guangzhou.

The model predicts the highest BI values in the provinces along the southern coast for the summer months and decreasing BI values with increasing latitude. Observations, however, show that BI values peak in more northern provinces, with BI> 30 in Hebei (bordering Beijing), Shandong and Henan provinces in August.

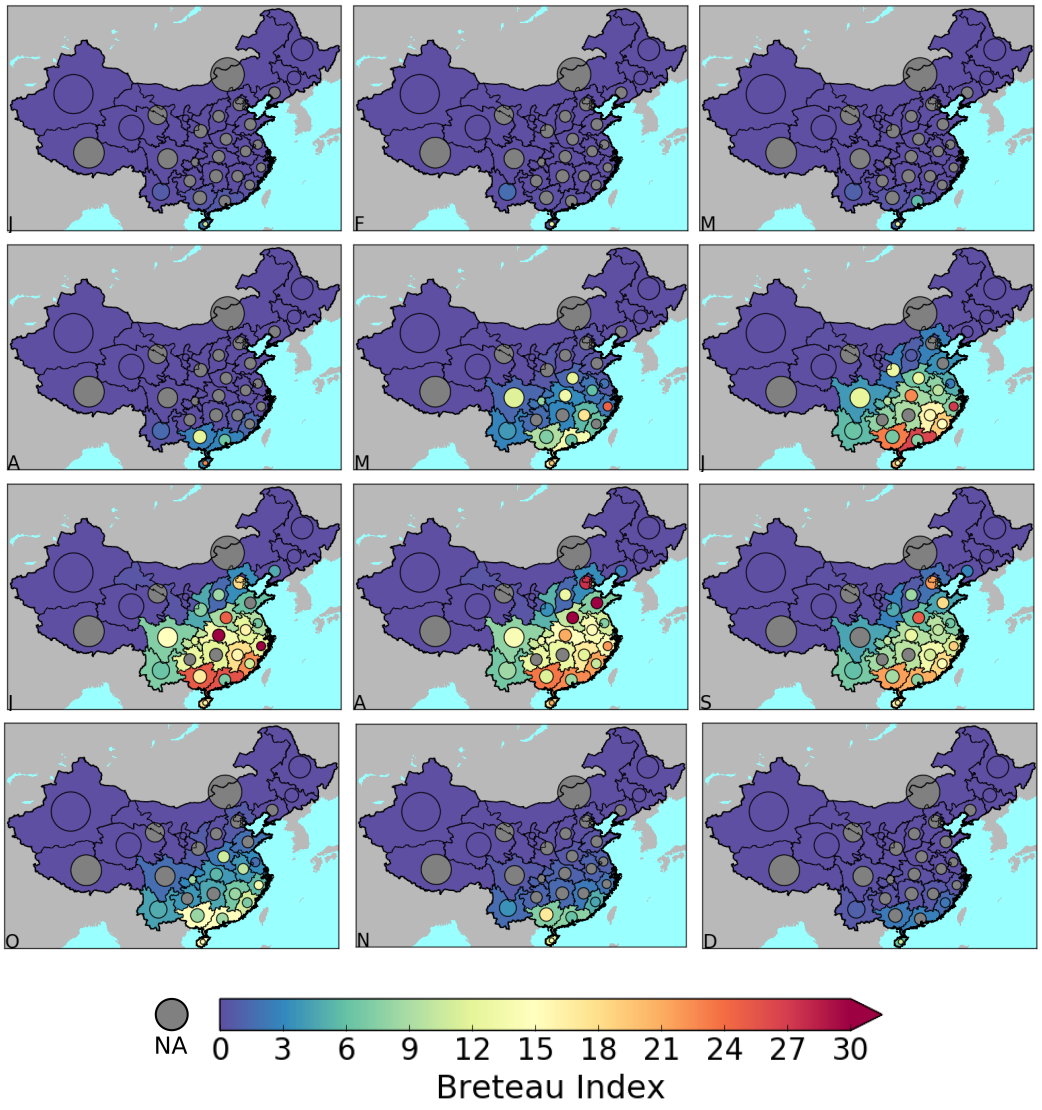

Figure 4.7: Monthly BI data for China 2015 Circle colour denotes the measured BI, grey for NA. Circle size relates to province size. Background colour of provinces denotes the simulated BI as the average of all weather station locations within province boundaries. A scaling factor of $a = 0.001$ was used for equation (4.4).

An explanation for this discrepancy might be that 2014 and 2015 saw heavy mosquito control actions especially in the southern provinces which skews the results. Recording of BI values might also focus on locations with known mosquito populations and thus not represent an averaged random sample that is used to calculate the modelled BI. Spearman's $\rho = 0.82$ for absolute BI values and Pearson's $r = 0.49$ for first-differences.

4.3.2 Guangzhou Dengue Outbreak

Figure 4.8 shows the number of weekly cases during the 2014 dengue outbreak in the Guangzhou area. In response to the ongoing outbreak, mosquito control measures or interventions (container emptying and fumigation with chemical treatments) were ordered. These were applied sporadically in the summer months and then continuously throughout October and November (Cheng et al., 2016).

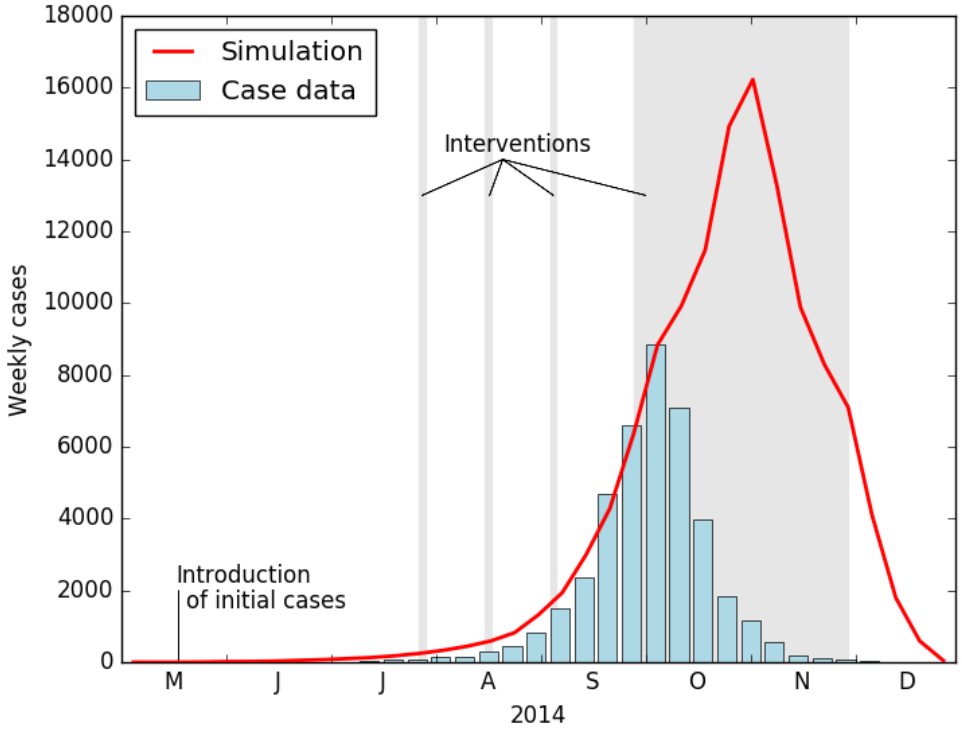

Figure 4.8: Guangzhou dengue cases Number of weekly human dengue cases during the 2014 dengue outbreak (blue bars) and simulated weekly cases (red line). Grey shades indicate officially ordered interventions to control the mosquito population.

Using the DDE model to simulate the infection dynamics gives very realistic weekly case numbers during the first half of the outbreak. After an introduction of infected humans in mid-May (1000 cases into a population of 13 million), the number of weekly cases is slowly increasing throughout June, July and August before seeing a steep increase in September. While actual case numbers went down from October on, possibly due to the intervention effort, simulated case numbers continue to climb up for another four weeks until unfavourable climate conditions stopped the outbreak naturally.

Looking at the number of adult female mosquitoes during 2014 showed that an introduction of dengue cases in mid-May was immediately followed by a rapid increase in mosquito numbers, compare Figure 4.9. While May temperatures in Guangzhou are generally very suitable for *Ae. albopictus*, there has also been above-average rainfall in May 2014 that created additional

breeding sites. Mosquito numbers for 2014 where higher than the ten-year average particularly in June, August and September which might have added to the outbreak.

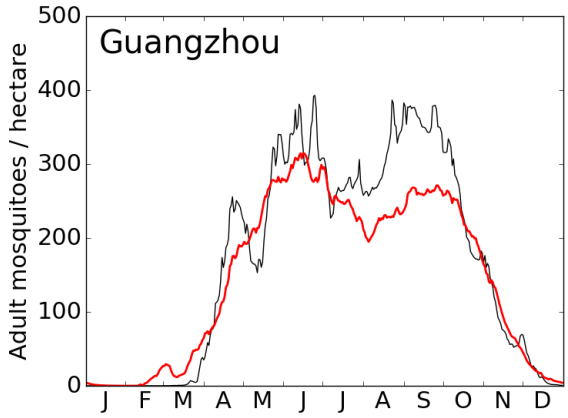

Figure 4.9: Guangzhou mosquito numbers Black: Modelled adult females during the dengue outbreak year 2014. Red: Average modelled adult females for the period 2006–2016. The month of May 2014 saw heavy rainfall that might have lead to the steep increase in mosquito numbers at the end of May.

4.3.3 Dengue Season Length

In a last step, the potential dengue season length for China was analysed. The whole human population was assumed to be infected constantly to simulate that every single emerging adult female can get infected, from the first in the season to the very last one. The maximal dengue season could then be defined as the period with at least one infected mosquito per hectare in this setting, approximately the situation from late April to mid-December in 2014 in Guangzhou.

Analysing the maximal dengue season for the whole of China shows that dengue transmission is possible nearly everywhere *Ae. albopictus* exists, see Figure 4.10 and compare Figure 4.3. The south coast of China including Guangzhou has a long maximal dengue season of about eight months. The further north, the shorter the maximal dengue season. Beijing only has about one month where dengue might be effectively transmitted. Some mountainous patches show up as having a much shorter dengue season.

Figure 4.11 shows that the maximum possible number of infected mosquitoes in Guangzhou starts to increase in April/May and decline to near-zero only in December. The curve shows a strong dip during the hot summer months. Jinan, a city with 8.5 million inhabitants, about 400 km south of Beijing, shows lower numbers and only a single peak in mid-summer. The maximal dengue seasons would be 4-5 months for Jinan and about 8 months for Guangzhou. Applying the same method to the UK, we see that London in comparison only has a very limited number of possible infectious mosquitoes in the warmest summer months. There would not be effective dengue transmission in London.

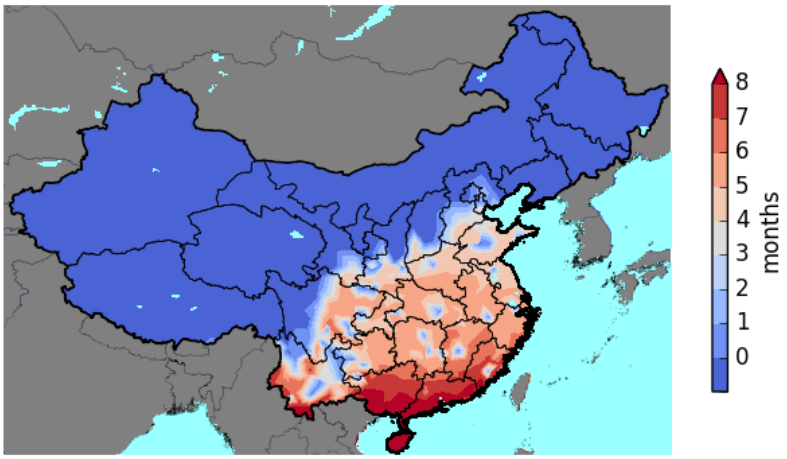

Figure 4.10: Dengue season in China Number of months with at at least one infected mosquito per hectare. Mean of 2010–2016 period.

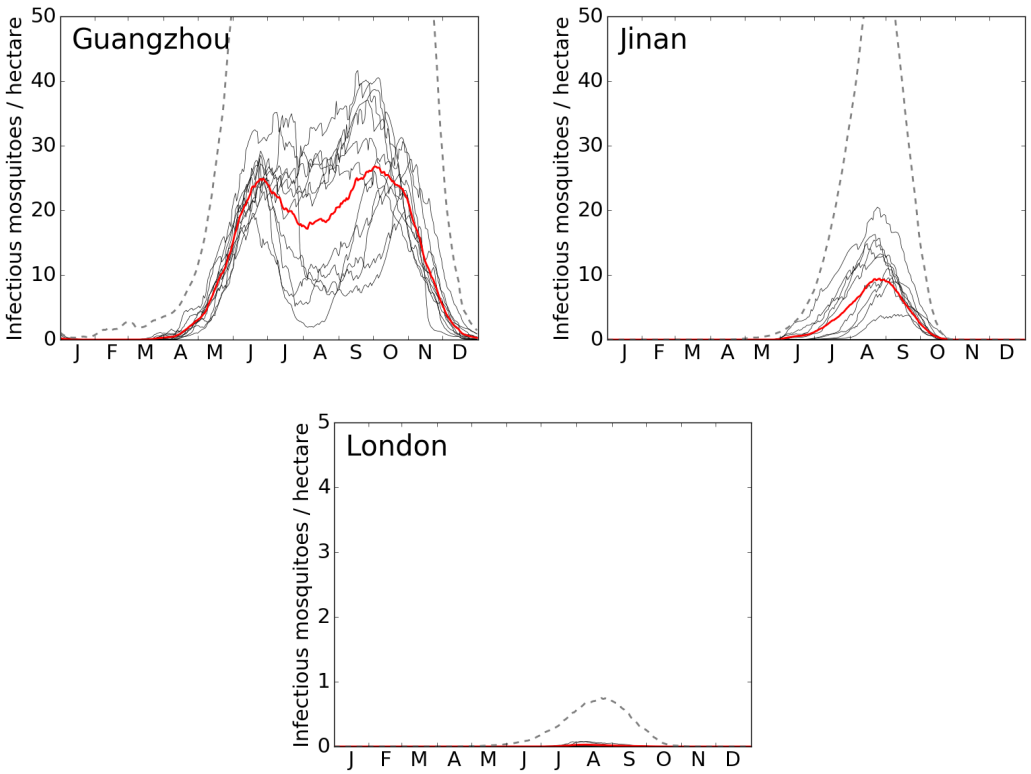

Figure 4.11: Infected mosquito numbers Black lines indicate simulations for individual years 2008–2016, the red solid line indicates the mean. Grey dashed lines indicate the equivalent ODE model means. Note the different scale for London.

We also repeated these simulation using the equivalent ODE model with identical parameters (compare section 2.2.1 and appendix A4.3). In comparison to the DDE model, the ODE model predicts higher mosquito numbers and longer maximal season length. Predicted season length for both Guangzhou and Jinan would increase by two month with the ODE model, numbers in

London stay only just below the threshold. More remarkably, though, is that the numbers for subtropical Guangzhou and Jinan would increase 4 to 5 fold during the summer months, while the increase for temperate London would be 30 fold. This uneven augmenting of numbers by the ODE model shows the importance of incorporating more realistic mechanisms for vector and virus development, especially for temperate regions.

4.4 Discussion

Vector populations and disease dynamics are difficult to predict from environmental factors. Using a novel stage-structured DDE model, we could realistically model the temperature-dependence of *Ae. albopictus*, its seasonal abundance and its role in dengue transmission in China. Note that in contrast to chapter 2, we did not include the rainfall driven egg hatching mechanism in the DDE model. However, such a mechanism could have improved our simulation results even further, especially for presence/absence predictions in arid areas such as the Taklamakan desert.

The predicted dengue season length for China corresponds well with the identified areas of dengue risk by CCC/CEPCC (2018). In these areas, the maximum number of infectious mosquitoes is greatest and potential outbreaks have the longest time to build up. Further north, the model still predicts dengue transmission up to Beijing. Shandong province, close to Beijing with about four months of possible transmission, just experienced a dengue outbreak in 2017 with about 200 cases (Li et al., 2019).

Looking at the 2014 dengue outbreak in Guangzhou, model simulations suggest that the outbreak could have reached much higher numbers if it was not for the officially ordered interventions. This is in accordance to other studies (Cheng et al., 2016; Zhu et al., 2019). While temperatures during the outbreak were not not exceptionally suitable for this region (Cheng et al., 2017), the early introduction of initial dengue cases that lead to a long build up of case numbers, which was only possible in these regions, has played a key role in the outbreak (Cheng et al., 2016).

Another key role in the outbreak was played by the disease vector *Ae. albopictus*. Li et al. (2018) could show that this mosquito is getting harder to control due to developed insecticide resistance. In contrast to Europe, *Ae. albopictus* is already present all over its full potential niche in China. It might nevertheless slightly spread in the future as warming temperatures render regions in the north and at higher altitudes more suitable, as the last decades have already done.

Its close relative, *Ae. aegypti*, that is even more competent to transmit dengue, is currently only present on Hainan island, Leizhou peninsula next to Hainan island and in Yunnan province (Jin and Li, 2008, and Xiaobo Liu, personal communication). However, urbanisation and warming temperatures help *Ae. aegypti* to spread further north and east (Li et al., 2014) and the future will probably see both *Aedes* species in Guangzhou and Guangdong province (Liu et al., 2019). This could lead to an increase of dengue outbreaks that burden the population as well as the economy (Wu et al., 2017; Fitzpatrick et al., 2017) and probably also affect other arboviruses circulating in China (Xia et al., 2017), including Zika (Liu et al., 2017) and Batai (Zhang et al., 2017).

Climate is one of most important factors for mosquito-borne disease transmission in China (Bai et al., 2013). While we tried to model the climate dependencies of mosquito and virus very

carefully, we had to neglect other possible impacts. These included socio-economic factors such as the regional GDP (Bi and Tong, 2014) but also the possibility for *Ae. albopictus* to pass on the dengue virus from adult female to egg (Guo et al., 2007). However, vertical virus transmission was unlikely to have impacted the 2014 outbreak (Sun et al., 2017).

While this model indicates the constant risk of dengue transmission, it can also indicate where and when *Ae. albopictus* populations build up to high numbers such as in the summer months in Guangzhou 2014. These mosquito hotspots could then be suppressed by targeted treatment before they experience an introduction of dengue (Unlu et al., 2016). Further research is needed to test whether this model is also able to forecast dengue hotspots, as for example the statistical model by Sang et al. (2015).

Following the results of chapter 2, London is the most probable place for *Ae. albopictus* survival in the UK. Applying the findings for Chinese metropolises to London, it can be seen that the numbers of possible infectious mosquitoes in London would be negligibly low. Though dengue transmission cannot be excluded completely, as individual mosquitoes could still get infectious, this is an unlikely scenario for now. Warming temperatures could, however, lead to more effective dengue transmission in the UK in the future (Liu-Helmersson et al., 2016). More temperate mosquito species such as *Culex pipiens* transmitting West Nile can be a greater risk for the UK already today (Ewing et al., 2016).

Chapter 5

Risk of arbovirus transmission in South America and Europe

The last decade has seen a number of extraordinary arbovirus outbreaks. Zika, a long known but understudied disease, emerged in Brazil in 2015 and caused a worldwide pandemic and the tropical diseases dengue and chikungunya started to appear in temperate Europe. Climate conditions are a determining factor for these disease outbreaks. The strong El Niño event in 2015 was for example suspected to have fuelled the Zika outbreak. Whether or not similar conditions led to the arbovirus transmission in Europe has not been analysed yet. Here, we use a climate-driven R_0 model that explicitly takes into account main vector species for all three diseases: *Ae. aegypti* and *Ae. albopictus*. We use global and regional temperature and rainfall data to analyse the Zika pandemic of 2015/16 and the risk of Zika, dengue and chikungunya transmission in Europe. We find that the Zika transmission risk was highly increased in South America during the outbreak due to exceptionally warm temperatures. In contrast, while Europe seems to be suitable for chikungunya and, to a lesser degree, dengue transmission in every year, we find the observed outbreaks were rather the result of unnoticed disease importations than exceptional climate conditions.

5.1 Introduction

Mosquito-borne diseases are one of the most challenging public health problems worldwide (Gubler, 2001; Mayer et al., 2017). They emerge in new regions, for example West Nile in the USA (Murray et al., 2010) or Usutu in Europe (Ashraf et al., 2015). Diseases including Japanese Encephalitis in Asia (Campbell et al., 2011) or dengue globally (WHO, 2009) are on the rise. The number of malaria cases, the biggest threat in terms of numbers, have been constantly decreasing in previous decades but did not go down in the last years any more (WHO, 2018). Other diseases that have been successfully controlled in the past are now experiencing a resurgence, such as yellow fever in Africa, which could spread again to the Americas or for the first time to Asia (Gubler, 2001; Wilder-Smith et al., 2017).

These emergences have multiple reasons: First, mosquito species that act as the main vectors have spread around the globe (Campbell et al., 2015). Second, the viruses or other pathogens themselves are transported by land, air and sea with infected humans or animals (Eckerle et al., 2018; Agapito et al., 2018). Third, environmental and climate change enables the vector establishment or simply the disease transmission in previously unaffected regions (Parham et al., 2015; Proestos et al., 2015). All these factors lead to completely susceptible populations suddenly being exposed to new diseases which makes them very vulnerable (Ferguson et al., 2016). Recent examples are the 2015 outbreak of Zika in Brazil that quickly spread to neighbouring countries (WHO, 2016*b*) and the emergence of locally acquired tropical disease cases including dengue and chikungunya in Europe in the last decade (Tomasello and Schlagenhauf, 2013; Venturi et al., 2017).

While we know that the prevailing climate is playing a major role in mosquito-borne disease outbreaks in general (Tabachnick, 2010; Chaves et al., 2012), it was not clear if the climatic conditions were key to the mentioned arbovirus outbreaks. It was for example assumed that the strong El Niño phenomenon of 2015, causing rainfall anomalies and warmer temperatures for the tropics, was partly responsible for the large scale of the Zika outbreak (Paz and Semenza, 2016; Monuz et al., 2016). While there was one big arbovirus outbreak in South America, possibly linked to warmer temperatures, there are years with only a few and years with a couple of hundred arbovirus cases in Europe. It is unclear whether these outbreaks were linked to certain climatic conditions or whether they could actually happen every year.

Here, we use a mathematical model originally developed by Turner et al. (2013) to estimate the basic reproduction number[1] during arbovirus outbreaks, i.e. the average number of secondary infections caused by a single infected individual in a completely susceptible population. The model includes the two main vector species *Ae. aegypti* and *Ae. albopictus* to explicitly account for different vectorial capacities and distributions. We will first calculate transmission risk during the Zika outbreak in Brazil in 2015, to analyse to what degree the El Niño phenomenon might have contributed to the outbreak. In a second step, we apply the developed model to estimate the risk of arbovirus transmission in Europe.

[1] Sometimes called basic reproduction ratio

5.2 Model & Methods

Based on the two vector - two host R_0 model by Turner et al. (2013), we built a two vector - one host R_0 model for the two mosquito vector species *Ae. aegypti* and *Ae. albopictus* and the human host, representing an extension of what is commonly known as a Ross-Macdonald model (Smith et al., 2012). The disease cycle in the vector is modelled with susceptibles, exposed and infected individuals, S_v, E_v, I_v. Susceptible mosquitoes can bite an infected human with the biting rate a, multiplied by the biting preference for humans, Φ. They get infected with a probability of β and, after the extrinsic incubation period , EIP $= \frac{1}{\nu}$, change to the infected state. All mosquitoes, $N_v = S_v + E_v + I_v$, suffer from a natural mortality rate of μ and reproduce with a rate of ρ. All parameters depend on the vector species and virus, see Table 5.1 for Zika and Table 5.2 for chikungunya and dengue.

The disease cycle in the human host is modelled with susceptibles, infected and recovered individuals, S_h, I_h, R_h. Here, susceptible humans can get bitten by an infected mosquito, which depends on the mosquito's biting rate, its host preference, the vector-to-host ratio, m, and the chance the mosquito is infected: $a\,\Phi\,m\frac{I_v}{N_v}$. The human host then gets infected with a probability b, and after depending on an infectious period with symptoms, recovers from the disease with a rate r.

The resulting equation system is given by

$$\begin{aligned}
\tfrac{d}{dt}S_{v_i} &= \rho_i\, N_{v_i} - a_i(T)\,\beta_i\,\Phi_i\frac{I_h}{N_h}S_{v_i} - \mu_i(T)\,S_{v_i}\\
\tfrac{d}{dt}E_{v_i} &= a_i(T)\,\beta_i\,\Phi_i\frac{I_h}{N_h}S_{v_i} - \nu_i(T)\,E_{v_i} - \mu_i(T)\,E_{v_i}\\
\tfrac{d}{dt}I_{v_i} &= \nu_i(T)\,E_{v_i} - \mu_i(T)\,I_{v_i}
\end{aligned}$$

for the vectors with $i = 1$ for *Ae. aegypti* and $i = 2$ for *Ae. albopictus*, and

$$\begin{aligned}
\tfrac{d}{dt}S_h &= -\sum_i \left(a_i(T)\,b_i\,\Phi_i\,m_i\frac{I_{v_i}}{N_{v_i}}\right) S_h\\
\tfrac{d}{dt}I_h &= \sum_i \left(a_i(T)\,b_i\Phi_i\,m_i\frac{I_{v_i}}{N_{v_i}}\right) S_h - r\,I_h\\
\tfrac{d}{dt}R_h &= r\,I_h
\end{aligned}$$

for the human host. Mosquito mortalities, biting rates, and the EIPs are temperature-dependent.

Following Turner et al. (2013), this differential equation system can be reduced to the basic reproduction number R_0:

$$R_0 = \sqrt{R_1 + R_2}$$

with

$$R_1 = \left(\frac{b_1\,\beta_1\,a_1^2}{\mu_1}\right)\left(\frac{\nu_1}{\nu_1+\mu_1}\right)\left(\frac{\Phi_1^2\,m_1}{r}\right)$$
$$R_2 = \left(\frac{b_2\,\beta_2\,a_2^2}{\mu_2}\right)\left(\frac{\nu_2}{\nu_2+\mu_2}\right)\left(\frac{\Phi_2^2\,m_2}{r}\right)$$

being the individual contributions of vector species 1 and 2 to the basic reproduction number R_0.

5.2.1 Zika in Brazil

To model transmission risk during the Zika outbreak in Brazil, the R_0 model can be parametrised for the vector species *Ae. aegypti* and *Ae. albopictus* and the Zika virus, see Table 5.1. Details on parameter estimation are given in appendix A5.2.

Table 5.1: R_0 model parameters Derivation and references of parameters are shown in appendix A5.2.

	Parameter	**Value/Formula**
a_1	Biting rate (1/day)	$0.0043\,T + 0.0943$
a_2		$0.5\,(0.0043\,T + 0.0943)$
Φ_1	Vector preference	1
Φ_2		0.5
b_1	Transmission probability V→H	0.5
b_2		0.5
β_1	Transmission probability H→V	0.1
β_2		0.033
μ_1		$\begin{cases}(1.22 + \exp(-3.05 + 0.0.72\,T))^{-1} + 0.196 & \text{for } T < 22°C \\ (1.14 + \exp(51.4 - 1.3\,T))^{-1} + 0.192 & \text{for } T \geq 22°C\end{cases}$
μ_2	Adult mosquito mortality rate (1/day)	$\begin{cases}(1.1 + \exp(-4.04 + 0.576\,T))^{-1} + 0.12 & \text{for } T < 15°C \\ 0.0003394\,T^2 - 0.01889\,T + 0.336 & \text{for } 15°C \leq T < 26.3°C \\ (1.065 + \exp(32.2 - 0.92\,T))^{-1} + 0.07476 & \text{for } T \geq 26.3°C\end{cases}$
$1/\nu_1$	Extrinsic incubation period, EIP (days)	$4 + exp(5.15 - 0.123\,T)$
$1/\nu_2$		$1.03\,(4 + exp(5.15 - 0.123\,T))$
P_1	Probability of vector existence	$[0-1]$
P_2		$[0-1]$
m_1	Vector to host ratio	$1000\,P_1$
m_2		$1000\,P_2$
r	Human recovery rate (1/days)	1/7

In general, *Ae. aegypti* is believed to be a much more competent arbovirus vector compared to *Ae. albopictus*, due to its higher biting rate and higher virus transmission probabilities. It also has a higher (almost exclusive) preference to bite humans, here set to 100%. *Ae. albopictus*

is more opportunistic though and also feeds on other animals. We assume that other animals are always present, whether the location is in an urban or rural area, so that *Ae. albopictus* will only chose human hosts in 50% of biting opportunities. The vector-to-host ratios, m_i, were estimated by taking the probabilities of vector occurrence P_i from Kraemer et al. (2015), multiplied by a constant, here $m_i = 1000\,P_i$.

To run temperature-dependent parameters, we used the monthly global climate data set GHCN CAMS with a 50 km × 50 km spatial resolution (Fan and van den Dool, 2008). We used the monthly precipitation data set GPCC with a similar resolution (Schneider et al., 2014) to mask areas with less than 80 mm rainfall for five months. This was done to mask regions in the Sahara and other deserts where arbovirus transmission is very unlikely. These regions have a relative high probability of vector presence according to Kraemer et al. (2015), and would thus have a high risk of Zika transmission when included.

5.2.2 Arboviruses in Europe

In a second step, we use the same model approach to analyse the transmission risk of mosquito-borne diseases in Europe. Here, *Ae. aegypti* can be eliminated as vector from the equations as this species is only present east from the Black Sea and on Madeira, a Portuguese archipelago off the coast of Morocco. The simplified R_0 model is given in appendix A5.1. In addition, a more realistic vector-to-host ratio can be used in Europe as we have year-round estimates for *Ae. albopictus* numbers, derived with the diffusion model in chapter 3. Vector numbers can then be related to human population density numbers to give a more appropriate vector-to-host ratio.

Besides Zika, two other viruses can be (and have been) transmitted by *Aedes* mosquitoes in Europe: dengue and chikungunya. The model is thus run with varying parametrisations according to each of the three viruses and parameters specific to dengue and chikungunya are shown in Table 5.2.

Table 5.2: Additional R_0 model parameters for *Ae. albopictus*. Derivation and references of parameters are shown appendix A5.2.

	Parameter	**Value/Formula DENV**	**Value/Formula CHIKV**
b	Transmission probability V→H	0.31	0.6
β	Transmission probability H→V	0.5	0.7
$1/\nu$	Extrinsic incubation period, EIP (days)	$4 + exp(5.15 - 0.123\,T)$	$1 + exp(5.15 - 0.123\,T)$
V	Adult mosquito density (1/km^2)	$\mathbb{R}^+$	
H	Human host density (1/km^2)	$\mathbb{R}^+$	
m	Vector to host ratio	$\frac{V}{H}$	
r	Human recovery rate (1/day)	1/5	1/7

In order to get vector-to-host ratios in the range of 1-35 females per person (Poletti et al., 2011; Manica et al., 2017), the vector life cycle model was run with a carrying capacity parameter downscaled by the factor 10 compared to chapters 2 and 3, so that $\lambda = 10^5$. Though the original parametrisation gave good estimates for absolute mosquito numbers in certain locations

(compare section 2.2.2), it gave too high ratios when related to human population densities, especially in more rural areas.

E-OBS was used to run the vector spread model, see chapter 3 with section 3.2.2 for details. We also calculated monthly temperature means from the daily E-OBS data set, to run the R_0 model on a monthly basis. Human population density is based on the GPWv4 data set (Doxsey-Whitfield et al., 2015). While we masked desert areas in the global Zika model, it was not necessary to apply such a mask for model runs in Europe. Rainfall is already incorporated as a variable in the vector model, see section 2.2.1 for details, so that dry periods lead to fewer or no mosquitoes, thus leading to small R_0 values.

5.2.3 Validation

Validation for the Zika model in South America was undertaken by Cyril Caminade, see Caminade et al. (2017) for details.

To validate the model for arbovirus transmission in Europe, we are looking at two recent outbreaks of chikungunya in Italy; an outbreak with over 300 cases south of Ravenna in 2007, and an outbreak with nearly 500 cases in Anzio, south of Rome and in Rome itself in 2017. While mosquito numbers for the Rome region could be taken from the diffusion model output from chapter 3, the E-OBS climate data set was incomplete for the Ravenna region in 2007, see section 3.2.2 for details. We thus had to use the ERG5 Eraclito data set for the Emilia-Romagna region (Antolini et al., 2016), and used climate data from point "#01984" for south Ravenna. We ran the vector model with five years of build-up time to estimate mosquito numbers and subsequently the R_0 model to calculate transmission risk. Note that this estimate assumes a fully established mosquito population in Ravenna, while the spread analysis in chapter 3 suggests that *Ae. albopictus* had just reached this region by 2006 (it had not been established in Ravenna in 2000 (Romi, 2001)). In effect, true population numbers and subsequently R_0 values might be lower than predicted.

Figure 5.1 shows monthly modelled R_0 values for either period and region. Both modelled R_0 values are in similar ranges of estimates by Poletti et al. (2011) and Feng et al. (2019) for Ravenna and Manica et al. (2017) for Anzio, near Rome. For the Ravenna outbreak, Poletti et al. (2011) estimates the vector-to-host ratio, m, to range between 10 to 35 mosquitoes per human, and our model predicts $m = 12$ for the summer months. However, the authors use a slightly different R_0 model and parametrisation. Manica et al. (2017) derive their R_0 value directly from case data. Note that both Poletti et al. (2011) and Manica et al. (2017) estimate the number of human infections by a single infectious human for their like-to-like risk value (here $R_0^\star$), while this model estimates the average number of infected mosquitoes by a single infected human and vice versa. In order to adjust the two estimates, we have to take the square root: $R_0 = \sqrt{R_0^\star}$. See appendix A5.1 for details.

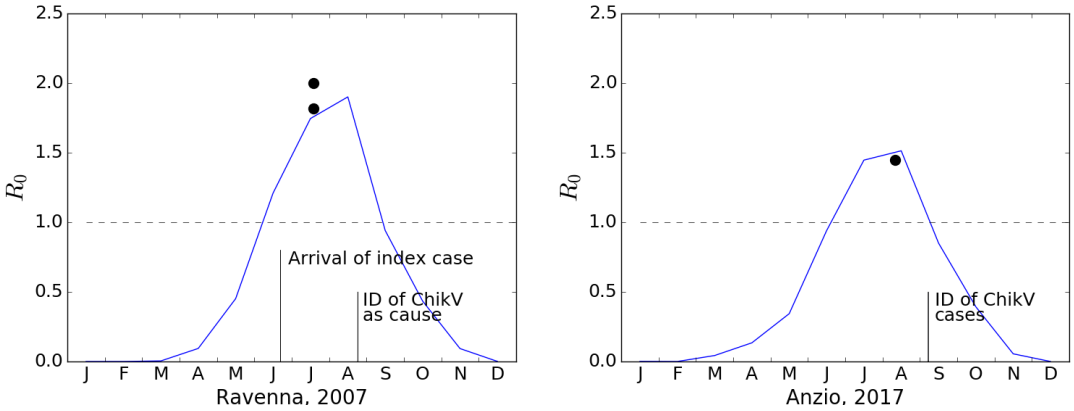

Figure 5.1: Model validation R_0 for chikungunya transmission for the Ravenna region in 2007 (left) and for Anzio, near Rome in 2017 (right). The blue line shows the modelled R_0 values, the dots show R_0 estimations by Poletti et al. (2011), Feng et al. (2019) and Manica et al. (2017), respectively.

5.3 Results

5.3.1 Zika in Brazil

First, we look at the worldwide Zika pandemic 2015/2016, running the model with both vector species. Figure 5.2 shows global peak R_0 values for the year 2015. India, sub-Saharan Africa and South America show very high risks of Zika transmissions, with R_0 exceeding values of 6. In the US and China, transmission risk can still be high, while Europe shows the lowest risk of all continents. Countries and regions where Zika had been previously reported, e.g. Uganda, Nigeria, India, south-east Asia (Hayes, 2009; Kindhauser et al., 2016) appear as suitable for Zika transmission too.

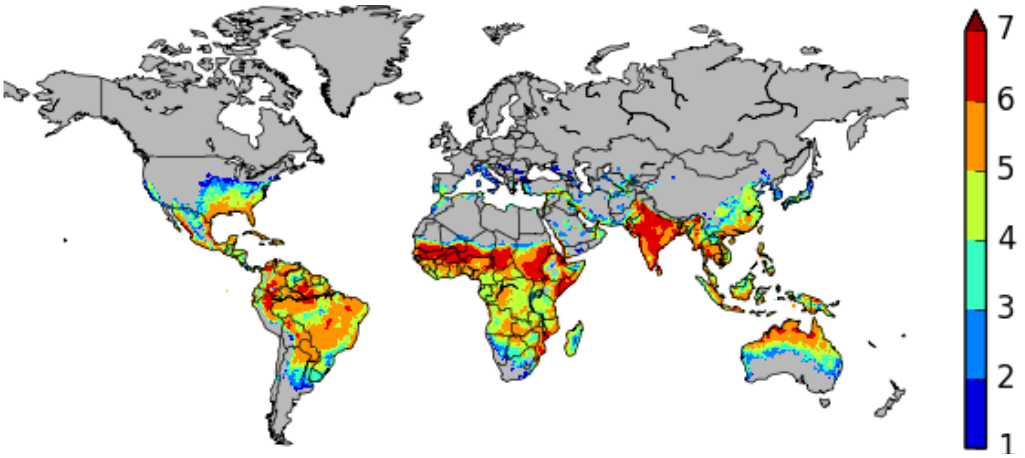

Figure 5.2: Global R_0 for ZIKV 2015 Maximum R_0 for 2015, masked where $R_0 < 1$. North-east Brazil experiences a high transmission risk, with R_0 values up to 5 or 6. Vector-to-host ratios $m_i = 1000\,P_i$ were used for the global model.

The Americas were most heavily affected during the Zika epidemic; Brazil, the epicentre reported more than 200,000 cases in 2016 (with many more suspected) (PAHO/WHO, 2017) and almost all other American countries reported locally transmitted cases (PAHO/WHO, 2017). Exceptions were only Canada, Chile and Uruguay that also show no risk in the model. All other countries show very high transmission risk with at least some regions in each country experiencing an $R_0 > 4$. Zika also spread to countries in Asia (Thailand, Vietnam and Singapore), causing a couple of hundred cases in each (Ho et al., 2017; Ruchusatsawat et al., 2019). These countries also show a high risk of Zika transmission in the model results. Seasonal R_0 values, showing the spatial shift in transmission risk hotspots, can be seen in appendix A5.3.

Figure 5.3 shows the R_0 anomaly of 2015 compared to the 1980 to 2015 period. It can be seen that 2015 was a particularly suitable year for Zika transmission, most continents experiencing higher R_0 values than usual. Regions showing particular increased transmission risk were Eritrea and Angola in Africa and Ecuador in South America. Brazil experienced a transmission risk in 2015 that was about 5 to 10% higher than usual. This anomaly can be explained by higher than normal temperatures on the South American continent, caused by an exceptionally strong El

Niño in 2015 (Monuz et al., 2016). Temperate regions (northern US, Europe, northern China) are masked as the yearly mean R_0 value was lower than 1. South-east Europe, though masked, experienced 20% higher R_0 values than usual, caused by a very hot summer all over Europe that year.

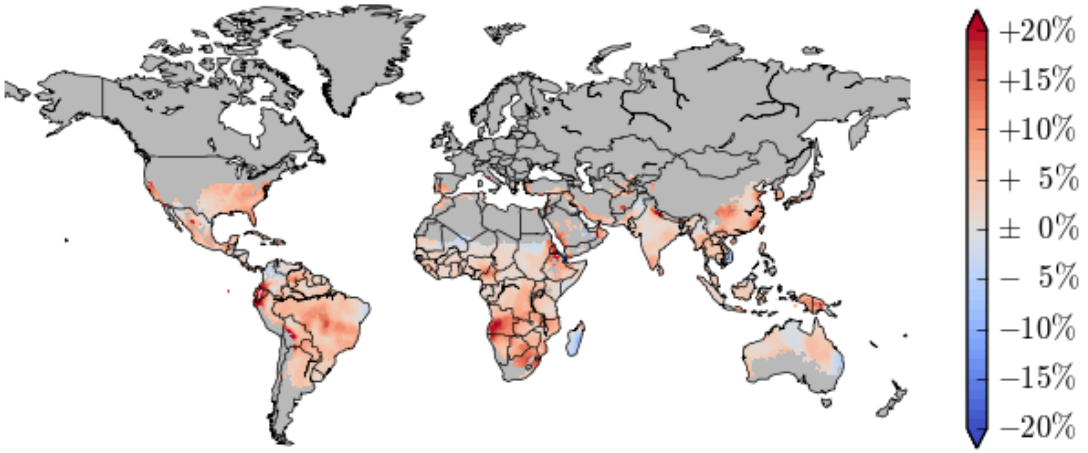

Figure 5.3: Global R_0 anomaly 2015 Mean R_0 of 2015 compared to baseline mean R_0 of 1980 to 2015, masked where $R_0 < 1$. Deep red colours indicate an increase of R_0 in 2015 by 20% or more compared to the average, blue colours indicate lower R_0 values than on average.

5.3.2 Arboviruses in Europe

Zika

Contrary to the findings with the global R_0 model used in section 5.3.1, the analysis with the updated model finds that R_0 values for Zika transmission do not exceed a value of 1 in any year, see Figure 5.4. Maximum R_0 values for Europe range between 0.3 and 0.4. It should be mentioned that an $R_0 < 1$ does not exclude local transmission, which is always possible when the virus is introduced to a place where a vector species is present. However, a spread of Zika in the population is very unlikely and no case of Zika that was mosquito-transmitted in Europe has been reported so far, despite large numbers of imported cases (ECDC, 2018*c*).

The difference to the global R_0 model is explained by the different approach to estimate the vector-to-host ratio m. With a probability of occurrence of 0.5 over Spain, France and Eastern Europe, to nearly 1 in Italy according to Kraemer et al. (2015), we assume a constant vector-to-host ratio of 500 to 1000 mosquitoes per person in southern Europe. Using the vector model to estimate mosquito numbers, we yield vector-to-host ratios that range between 0 and 50 mosquitoes per person, depending on the season, which might be more realistic (Poletti et al., 2011; Carrieri et al., 2012). This shows that the global R_0 model, which was calibrated to South America, might not be applicable to temperate regions equally well.

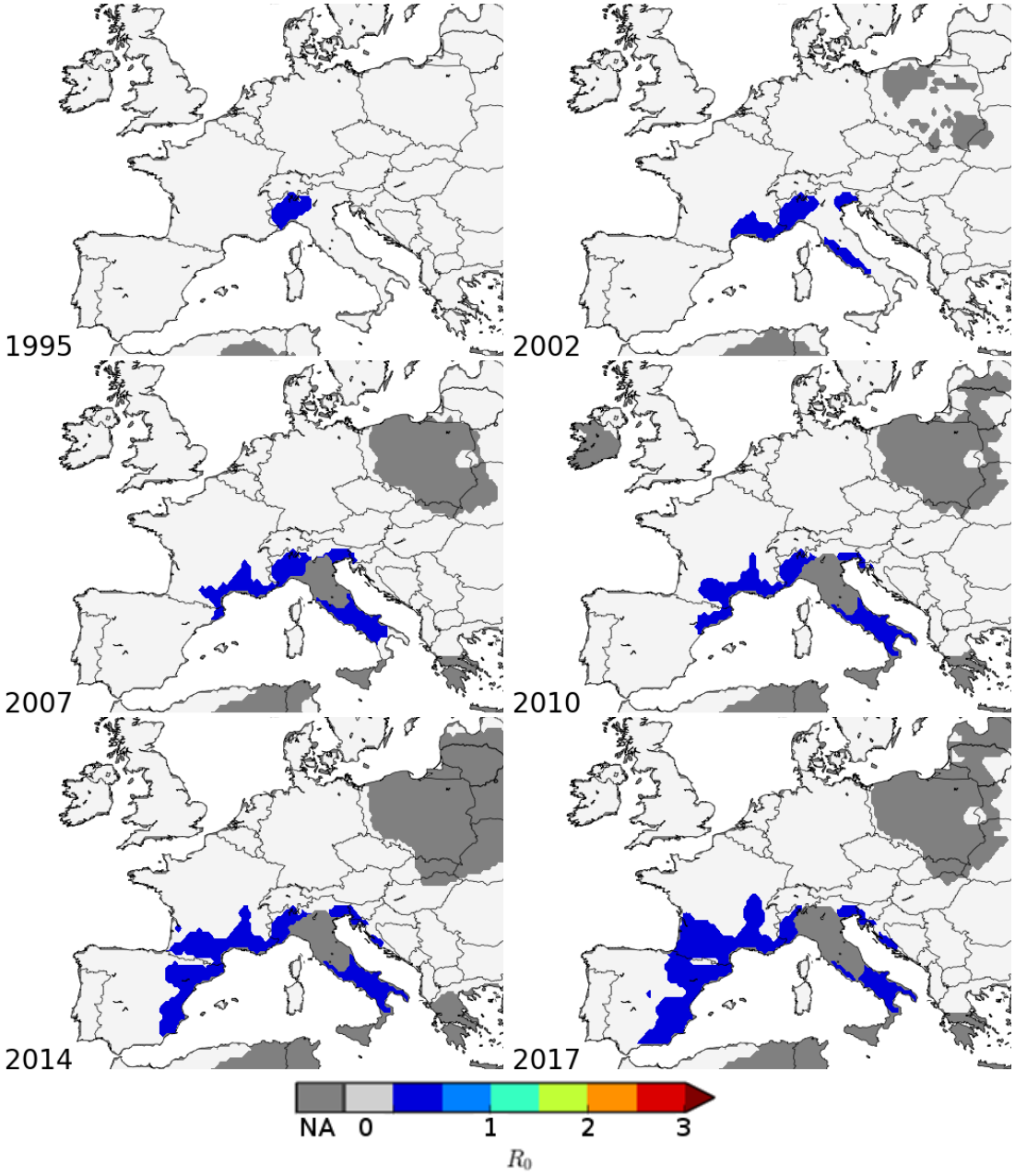

Figure 5.4: Risk of Zika transmission in Europe The maximum R_0 values do not reach 1 in any displayed year because *Ae. albopictus*' has a low transmission efficiency for the Zika virus.

Dengue

Dengue transmission is more likely than Zika transmission in Europe, due to *Ae. albopictus*' higher probability of becoming infected and infectious with dengue compared to Zika. Maximum R_0 values typically reach values around 1 and in some locations up to 2, see Figure 5.5. This elevated (but still low) risk of transmission is visible in dengue cases in the last ten years. 2010 and 2014 saw 6 and 4 cases in France and Croatia, 2013, 2015 and 2018 saw 1, 7 and 4 cases, respectively in southern France and Spain (not shown) (ECDC, 2017, 2018*d*). A bigger outbreak

of dengue occurred on the Portuguese island Madeira in 2012 with about 2 100 cases, but was caused by *Ae. aegypti* and not *Ae. albopictus* (ECDC, 2013).

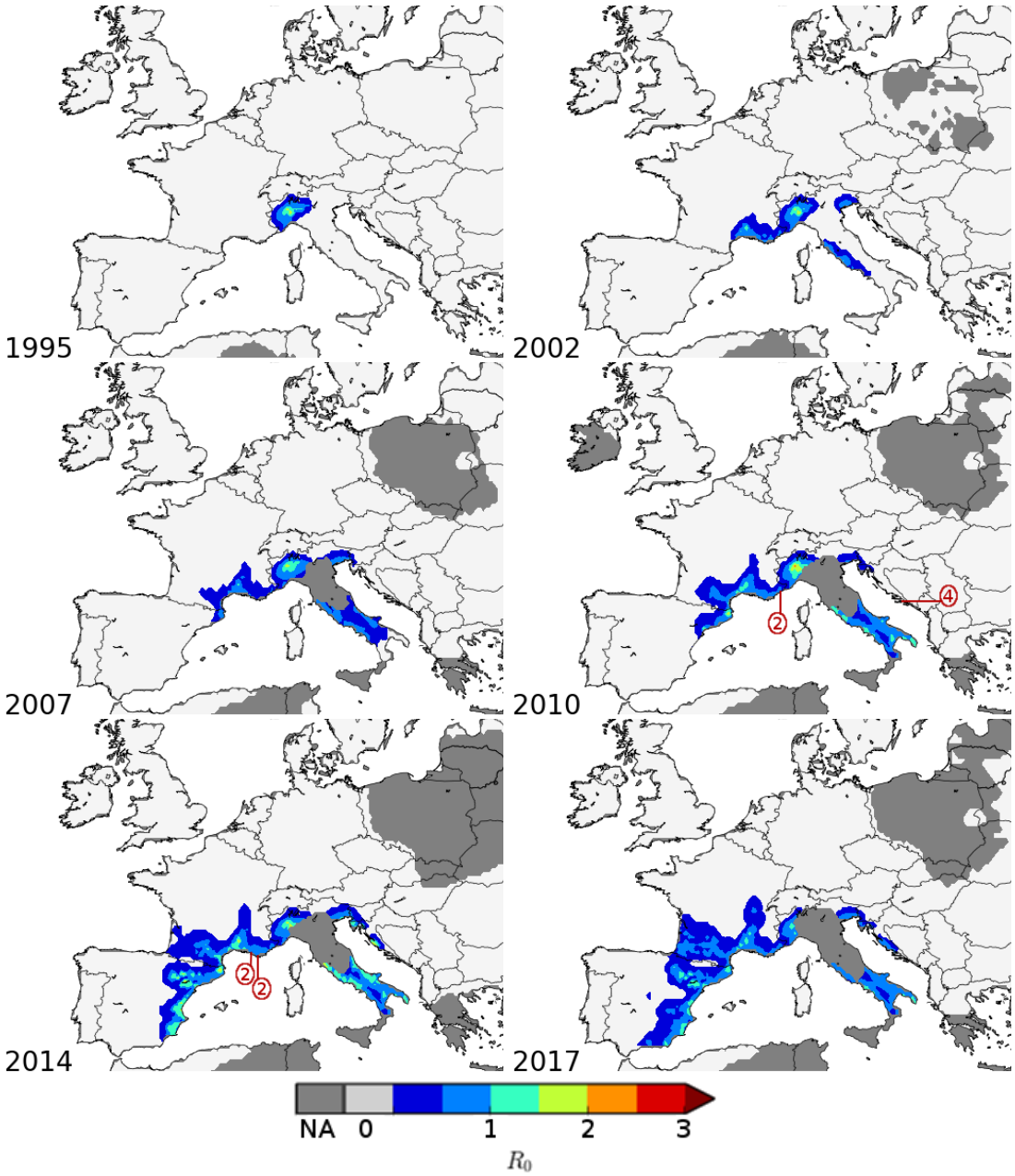

Figure 5.5: Risk of dengue transmission in Europe Plotted are the maximum R_0 values for each year, typically for the warmest month of July or August. Maximum R_0 values for dengue transmission often reach values between 1 and 2. Numbers in red circles denote reported dengue cases according to ECDC (2018*d*).

Chikungunya

Due to *Ae. albopictus*' high vector competence for chikungunya (high infection probability, low EIP), the analysed transmission risk in Europe is highest for this arbovirus. Most years see peak

R_0 values between 2 and 3, see Figure 5.6 and every year since 1993 experiences local R_0 values above 1. In contrast to Zika or dengue, chikungunya actually caused outbreaks with several hundred cases in Europe. Both outbreaks occurred in Italy, in 2007 and 2017, see section 5.2.3 for details. Chikungunya was also transmitted in France in several years (2010, 2014, 2017) but in smaller numbers (ECDC, 2017).

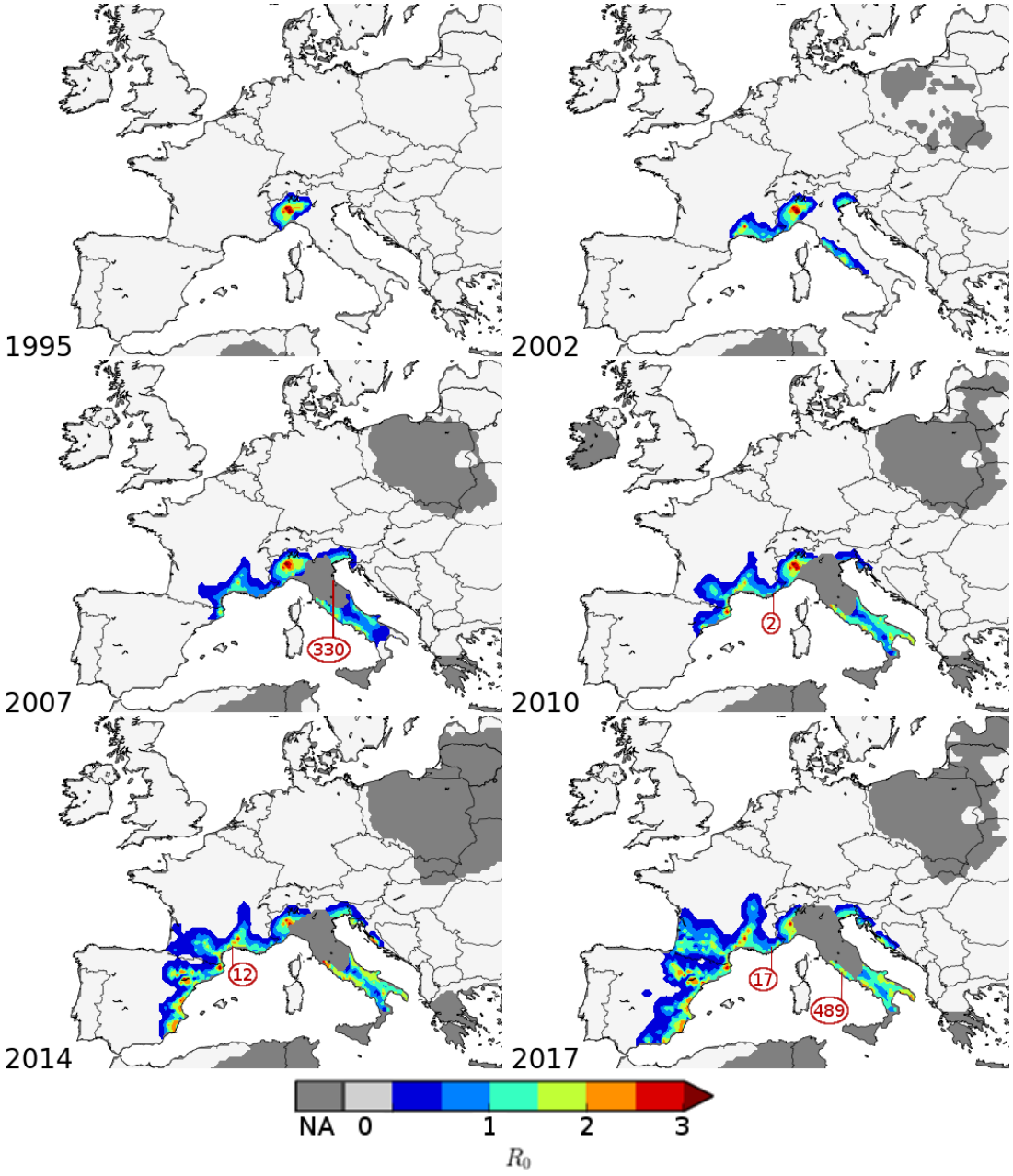

Figure 5.6: Risk of chikungunya transmission in Europe Maximum R_0 values for chikungunya transmission often exceed values of 3. Numbers in red circles denote reported chikungunya cases according to ECDC (2018*d*).

5.4 Discussion

We found that the Zika outbreak 2015 in Brazil was amplified by El Niño's exceptional weather conditions as previously suspected (Paz and Semenza, 2016). High R_0 values in previous years indicate, however, that the outbreak might have occurred in an extenuated form without a strong El Niño effect, or in previous years if the virus had been introduced earlier. Potential impacts of El Niño on other arbovirus outbreaks in 2015 such as the yellow fever outbreak in Angola (WHO, 2016*c*), or dengue outbreak in Taiwan and India (Wang et al., 2016; NVBDCP, 2016) are still to be examined further.

The transmission risk analysis for Europe shows that every year seems to be climatically suitable for arbovirus transmission. Summer R_0 values have been above 1 since 1995 in Italy, France, and lately Spain for chikungunya and to a lesser extent, for dengue. The two chikungunya outbreaks of 2007 and 2017 in Italy might just have been the concurrence of virus introductions into vector infested communities at the beginning of warm seasons. Other years (2009, 2012 and 2015) saw higher R_0 values in Europe, especially in Italy.

Europe constantly showed the highest risk for chikungunya, due to the virus' mutation that increases its transmission probability by the vector *Ae. albopictus* (Tsetsarkin et al., 2007). The risk for Zika was lowest, both vector species show a rather low competence for ZIKV (Chouin-Carneiro et al., 2016). Conversely, the risk for chikungunya and dengue is also high when ZIKV is effectively transmitted. It is thus of little wonder that the arbovirus outbreak in Brazil was actually a triple epidemic of Zika, chikungunya and dengue (Zanotto and Leite, 2018) which made diagnosis very difficult (Raquel Medialdea-Carrera, personal communication).

The transmission risk estimates for Europe are similar to what have been found for chikungunya and Zika in other studies (Guzzetta et al., 2015, 2016; Messina et al., 2016). Values for dengue are a bit lower than those estimated by Guzzetta et al. (2015) for northern Italy due to a different model parametrisation. Other dengue estimates for Europe seem too dependent on human population density and might not give enough weight to climate factors that drive mosquito development and EIPs (Rogers et al., 2014).

The discrepancy in the two Zika R_0 estimates with the global and the European model is due to different estimates of the vector-to-host ratio m. The Zika transmission risk is estimated to be up to $R_0 = 3$ with the global, but only $R_0 < 1$ with the European model. The rough approach of the global model reaches values of 500+ mosquitoes per human, while the approach based on mosquito estimates from chapter 3 works with values of approx. 10 to 20 mosquitoes per human (in the range estimated by Poletti et al. (2011)) and might be more realistic for temperate climates. The latter approach yields reasonable values during the summer months of chikungunya outbreaks: R_0 values between 1.3 and 1.9 in two villages near Ravenna on the Adriatic coast 2007 (compare $R_0 = 1.8$, resp. like-to-like $R_0^\star = 3.3$, and $R_0 = 2.0$ for Poletti et al., 2011; Feng et al., 2019) and between 0.9 and 1.5 in Rome 2017 (compare $R_0 = 1.4$, resp. like-to-like $R_0^\star = 2.1$ for Manica et al., 2017). However, our R_0 estimate might actually be too

high in the latter outbreak. Contrary to 2007, the virus strain from 2017 did not carry the E1-A226V mutation (Ciocchetta et al., 2018), and thus the vector competence for *Ae. albopictus* would have been lower than our model assumes.

While it is unlikely that anything will stop another chikungunya outbreak in Europe from happening, especially with warming temperatures (Fischer et al., 2013), the Zika outbreak will probably not repeat itself in Brazil in the near future. With large parts of the population having been exposed to the virus in the last years (PAHO/WHO, 2017; Haby et al., 2018), the acquired immunity could delay possible outbreaks for years (Ferguson et al., 2016; Lowe et al., 2018).

Looking at the UK, we see no threat of chikungunya, dengue or Zika transmission in past years, due to the absence of *Ae. albopictus*. While this vector species could be introduced and establish itself in the UK in the future (compare sections 2.3 and 3.3.2), the colder British climates will have two effects on the transmission risk: They will inhibit mosquito development so that the vector-to-host ratio will be much lower than in southern Europe, and they will inhibit the virus replication in the mosquitoes, making it unlikely for large arbovirus outbreaks to happen (Gould et al., 2006, and compare section 4.3). However, there is always the chance of individual cases as history has shown (Meers, 1986).

Chapter 6

Development of tropical and temperate *Aedes* mosquitoes at low temperatures

Several mosquitoes of the genus *Aedes* have been introduced to Europe in recent times. Most notably, the Asian tiger mosquito *Aedes albopictus* has rapidly extended its range, thereby encountering more unfavourable climatic conditions in the northern regions. But while several studies have analysed the influence of different temperatures on immature development to determine this species' climatic niche, this has only been done with tropical and subtropical strains. Development of the European strain, potentially adapted to colder climates, has not been tested before. Here, we analyse the cold-adaptation of European *Ae. albopictus* larvae, pupae, and adult females in comparison to a tropical strain under controlled laboratory conditions. Tropical *Ae. aegypti* are used for interspecies comparison. We find no difference in cold-temperature survival between temperate and tropical strains. We do, however, find a prolonged duration of the larval stage for the European strain, which might act as a mechanism to pass cold temperature spells in the resilient aquatic instead of the adult stage.

6.1 Introduction

Six invasive mosquito species of the genus *Aedes* have been introduced to Europe in recent decades (Medlock et al., 2012), three of which (*Ae. albopictus, Ae. japonicus, Ae. koreicus*) were able to establish themselves on the continent (ECDC Vectornet, 2019). To survive in Europe's seasonal climate, these species have to show some kind of adaptation to cold temperatures, especially the originally (sub-)tropical species *Ae. albopictus* and *Ae. aegypti*.

Some of these *Aedes* species produce eggs at the end of the warm season that go into a diapausing stage for overwintering (Miyagi, 1971; Kaufman and Fonseca, 2014). In addition to this mechanism in the egg stage, the larval stages have to be adapted to colder temperatures too. When the first larvae of *Ae. albopictus* hatch after the overwintering period, water temperatures are only 10-11 °C (Toma et al., 2003). Over the following spring months the population slowly builds up numbers. But cold spells during this period could severely decimate the population. Temperatures below 10 °C can lead to high larval mortality rates, especially in the fourth instar stage (Chang et al., 2007).

The two species that are most worrying to public health are *Ae. albopictus*, which has already established over large parts of Europe (ECDC Vectornet, 2019), and *Ae. aegypti*. In the past, *Ae. aegypti* was present nearly everywhere in the Mediterranean region (Holstein, 1967) but today it is only found on Madeira and around the Black Sea. Though it has been introduced into the Netherlands with used tyres (Scholte et al., 2010) and survives under an airport baggage terminal (Jolyon Medlock, personal communication), it is unlikely this species could establish in northern Europe as its eggs are not cold-resistant (Hanson and Craig, 1995). Both species are adapted to urban areas (*Ae. aegypti* more than *Ae. albopictus*), frequent human biters (Ponlawat and Harrington, 2005) and have been involved in various disease outbreaks (e.g. Rezza et al., 2007; Lourenço and Recker, 2014; Ai et al., 2016).

These two species have been studied extensively in laboratories. Growth rates and survival of the different developmental stages were measured under various temperature conditions (e.g. Lee, 1994; Delatte et al., 2009; Eisen et al., 2014) and Brady et al. (2013) undertook a meta-analysis on laboratory and field survival of both species. However, all these studies use non-European, mostly tropical strains in their experiments. The only exception to our knowledge is the study by Thomas et al. (2012) that looks at cold-adaptation in the egg stage of European *Ae. albopictus*. They showed that non-diapausing and diapausing eggs of an Italian strain have a lower temperature threshold after up to 24 h freezing compared to a tropical strain.

Given that mosquitoes can adapt in response to a change in temperature in as little as 10 years (Egizi et al., 2015), we hypothesise that the temperate strain of *Ae. albopictus*, introduced to Italy about 30 years ago, shows some form of cold-adaptation in its immature or adult stages. We test this by comparing the survival, development and biting behaviour of temperate and tropical strains at low temperatures. We also include the closely-related but more tropical *Ae. aegypti* for interspecies comparison.

6.2 Methods

We are comparing three mosquito populations:

- *Aedes albopictus* from temperate Italy
- *Aedes albopictus* from tropical Singapore
- *Aedes aegypti* from tropical Singapore

All colonies were only third generation (F3) lab raised, to avoid adaptation to laboratory conditions.

We reared the mosquitoes at constant temperatures of 12 °C, 15 °C, 18 °C and 24 °C for 125 days. Four incubators capable of heating and cooling (model MIR-154, Sanyo, Japan) were used for larvae, pupae and adults. Incubators were calibrated with temperature data loggers (model TGP-4017, TinyTags, UK) and showed an accuracy of ±1 °C.

Relative humidity, RH, could not be controlled by the incubator. We tried to keep it stable at each temperature by placing the same number of water pans in each incubator for the course of the experiment, but cooling incubators reduced the RH. RH was 28 % for 12 °C, 31 % for 15 °C, 99 % for 18 °C and 83 % for 24 °C. The day-night cycle was 12h:12h on average[1].

6.2.1 Mosquito Colonies

Both tropical mosquito strains were originally caught in Singapore (annual temperature nearly constant at 27 °C, 2000 mm annual rainfall). Colonies were kept at 27±1 °C, with RH between 60 and 80 % and a day-night cycle of 12h:12h until F3 generation. Mosquitoes for the temperate strain were originally caught in Italy (from the regions Puglia, Lazio and Emilia-Romagna, about 25 °C in summer, 0-5 °C in winter and 500-1000 mm annual rainfall). The colony was kept at 26±1 °C, with a RH above 70 % and a day-night cycle of 12h:12h. Eggs were obtained from the Department of Public Health & Infectious Diseases, University of Rome, and from the National Environment Agency in Singapore, respectively.

Eggs from all colonies were hatched at the same day but unfortunately eggs from the Italian strain had a zero hatching rate. We thus had to re-order temperate *Ae. albopictus* eggs and hatched them with a two week delay, so that the experimental lines for tropical and temperate strains were staggered by two weeks, with 16 weeks of running concurrently. Experimental conditions for all three strains were kept constant.

Larval Stage

Eggs were hatched in de-oxygenated water that was hay-infused for two days (Imai and Maeda, 1976). L1 larvae were transferred to rearing pans with 250 ml water. Two pans for each strain

[1] Unfortunately, the light cycle could not be controlled with the incubators either. We placed the incubators' windows so that each of them half-faced a laboratory window. At the beginning of the experiment in August, the day-night cycle started at approx. 14h:10h and was approx. 10h:14h at the end of the experiment in November.

and temperature were used as replicates, with 50 larvae each. Bottled water was used for the experiments (Ashbeck® mineral water, still). We had

$$4 \text{ temperatures} \times 3 \text{ strains} \times 2 \text{ replicates} \times 50 \text{ larvae} = 1,200 \text{ larvae}$$

in total. Larval development (time spent in each larval instar stage L1 to L4) and survival was checked on a daily basis on early mornings and recorded. Larvae were fed daily with ground TetraMin® fish food according to the feeding regimen displayed in Table 6.1. A third of the pans' water was replaced with fresh bottled water twice a week.

Table 6.1: Larval feeding regimen Larval numbers and instar stages were checked daily to calculate the food needed for each pan.

Instar	Food per larva
L1	0.04 mg/day
L2	0.1 mg/day
L3	0.2 mg/day
L4	0.32 mg/day

Pupal Stage

As soon as larvae reached the pupal stage, they were transferred into 100 ml tubs with fresh water. Tubs were loosely sealed with caps to allow airflow but prevent eclosing mosquitoes from escaping. Time from pupation to eclosion was checked on a daily basis and recorded with overall survival of the pupal stage.

Adult Stage

Adult females that eclosed over night were transferred from the 100 ml tubs into small cages (17.5 cm × 17.5 cm × 17.5 cm) that were also kept in the incubators. As incubator space was limited, we only used females from the two days on which most of the females emerged. At 18 °C and 24 °C, female emergence was highly synchronised so that we had two cages with 15 or more females for each strain. At 15 °C, survival to adulthood was already lower, and female emergence was more spread out, so that we only had cages with three or more females here. No female hatched at 12 °C.

Females in cages had constant access to a 10% sucrose solution and were daily offered a blood meal for 30 minutes. The Hemotek® system was used for feeding with ungulate blood (sheep or horse blood). Female mosquitoes that fed were removed from the experiment. Time to first blood meal and percentage fed was recorded. Females that did not feed for 31 days were removed from the experiments.

6.2.2 Statistics

To compare mean development times, we used the Wilcoxon rank sum test to check for differences between tropical and temperate *Ae. albopictus* trains. We used non-parametric tests as data was not normal-distributed. Differences in survival and blood-feeding between strains was tested with Fisher's exact test, as the sample size was small. Kaplan-Meier curves (Kaplan and Meier, 1958) and restricted mean survival time (RMST) (Royston and Parmar, 2013) were used to analyse differences in daily larval mortality. We did not use the standard Cox Hazard model as its assumption of proportional hazards was not met and thus test can have a low power (Tian et al., 2018). After comparing the *Ae. albopictus* strains, we compared development and survival of the *Ae. aegypti* strain against the pooled *Ae. albopictus* strains. Statistical analysis was carried out using R.

6.3 Results

We will first compare the European with the tropical *Ae. albopictus* strain, for larval, pupal and blood-feeding female stages separately. We will then pool both *Ae. albopictus* strains and compare their development, survival and feeding behaviour with those of *Ae. aegypti*.

6.3.1 Temperate vs. Tropical *Ae. albopictus*

Larval Stage

No larvae of any of the populations developed into pupae at 12 °C. All but one larva died before the end of the experiment at day 126.

The tropical *Ae. albopictus* strain shows a significant faster development at 15, 18 and 24 °C (Wilcoxon, $N = 195, 274$ and 275, resp., $p < 0.001$ each). Total survival was similar between strains, with a slight difference at 24 °C (Fisher, $N = 200, p = 0.04$), see Figure 6.1. One replicate of the temperate *Ae. albopictus* strain at 18 °C showed nearly 100% mortality in the first couple of days and was thus excluded from the analysis.

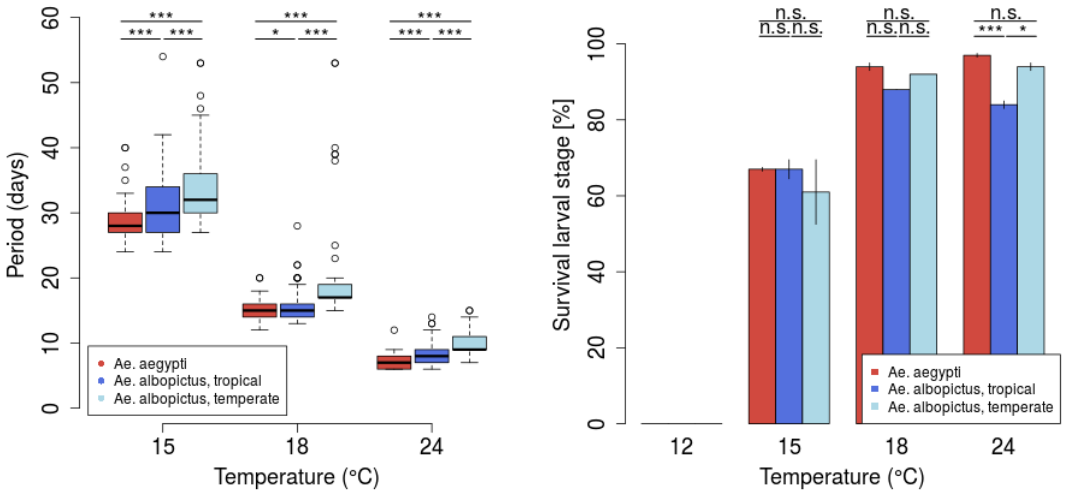

Figure 6.1: Larval stage Left: Time from hatching to pupation. Right: Survival of larval stage with standard error of two replicates as error bars. Symbols over crossbars denote significance level: n.s.: not significant, *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$.

Survival curves for larval stages at each temperature are shown in Figure 6.2. Temperate *Ae. albopictus* had a significantly higher restricted mean survival time, RMST, at 12 °C with $\text{RMST}_{\text{temp}} = 15.9$ days and $\text{RMST}_{\text{trop}} = 10.7$ days ($N = 200, p = 0.024$). The temperate strain also had a slightly higher RMST at 24 °C ($N = 200, p = 0.002$) but did not differ significantly at other temperatures.

Mean development times and survival for each larval stage, L1, L2, L3 and L4, are given in Table A6.2 and A6.3 in the appendix.

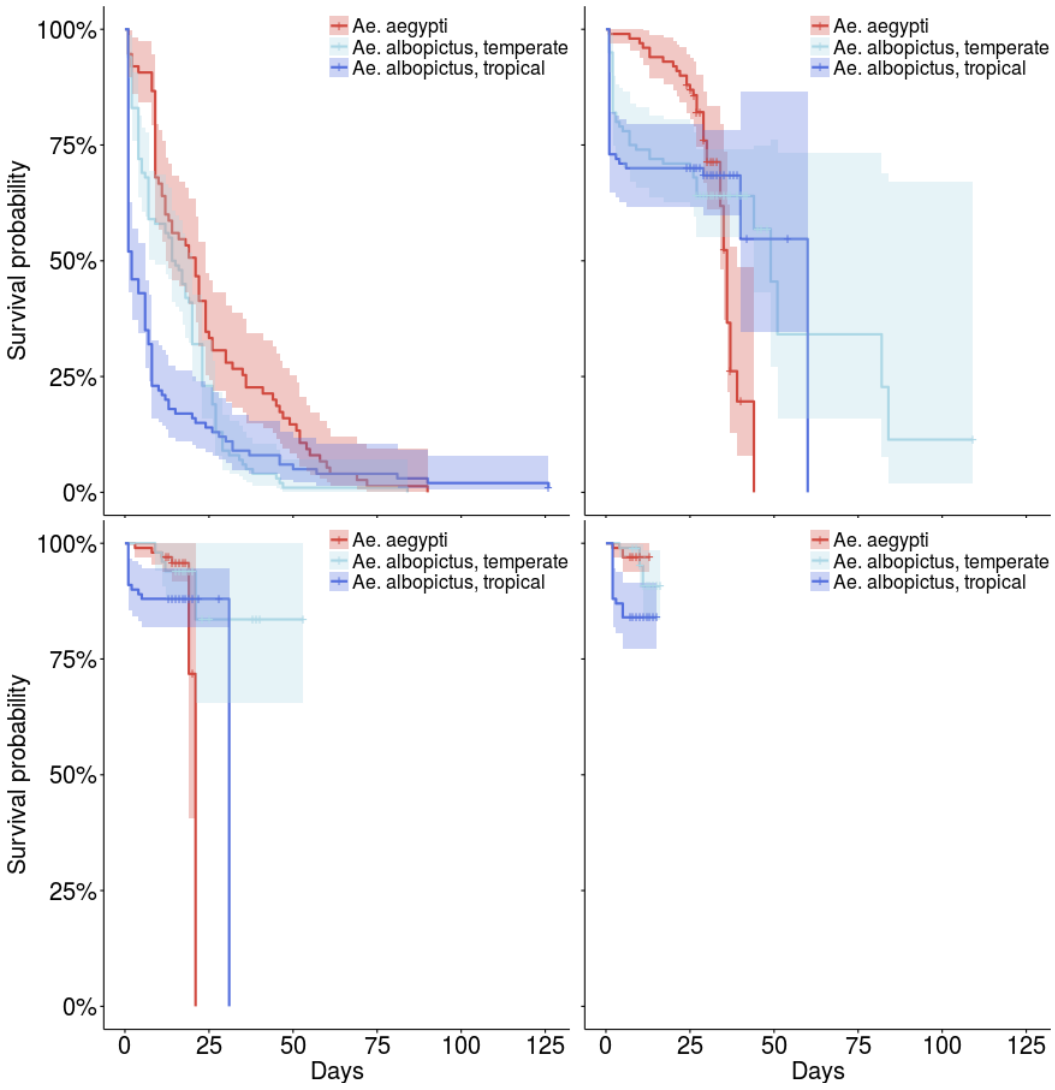

Figure 6.2: Larval survival Kaplan-Meier analysis of survival rates at four different temperatures: 12 °C (topleft), 15 °C (topright), 18 °C (bottomleft) and 24 °C (bottomright). Censored data (larvae undergoing pupation) are indicated by crosses. A survival probability dropping to zero means that the last larvae has died instead of undergoing pupation. Half the L1 larvae of one *Ae. aegypti* replicate at 12 °C were accidentally killed at day 1 of the experiment, so that we had pans at 50 and 25 larvae for this strain instead.

Pupal Stage

At 15 °C, the tropical *Ae. albopictus* has a slightly lower mean pupation period of 8.9 days, compared to the temperate strain with 9.1 days (Wilcoxon, $N = 128, p = 0.02$). Time to eclosion at other temperatures was similar, see Figure 6.3 (left). The tropical strain has a significant higher survival at 18 °C and 24 °C (Fisher, $N = 134, p = 0.004$ and $N = 178, p < 0.001$, resp.), see Figure 6.3 (right).

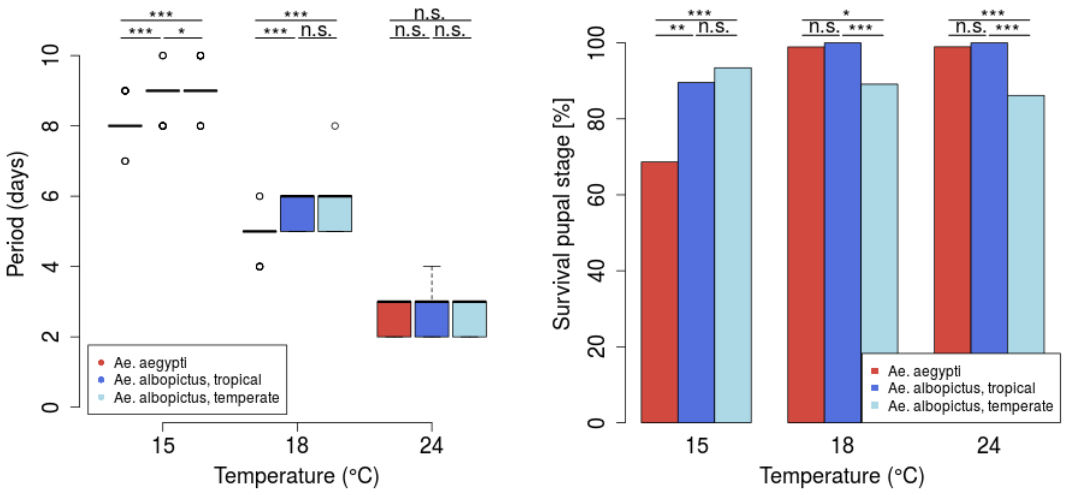

Figure 6.3: Pupal stage Time and survival from pupation until eclosion. Symbols over crossbars denote significance level: n.s.: not significant, *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$.

Juveniles (Larvae and Pupae Combined)

Comparing the development from egg hatching until adult emergence (L1 - A) shows the same picture that became clear for larvae and pupae separately; the tropical *Ae. albopictus* strain develops faster than the temperate strain at all temperatures, see Figure 6.4. Survival of the complete aquatic stage does not show any significant difference at any temperature for these two strains.

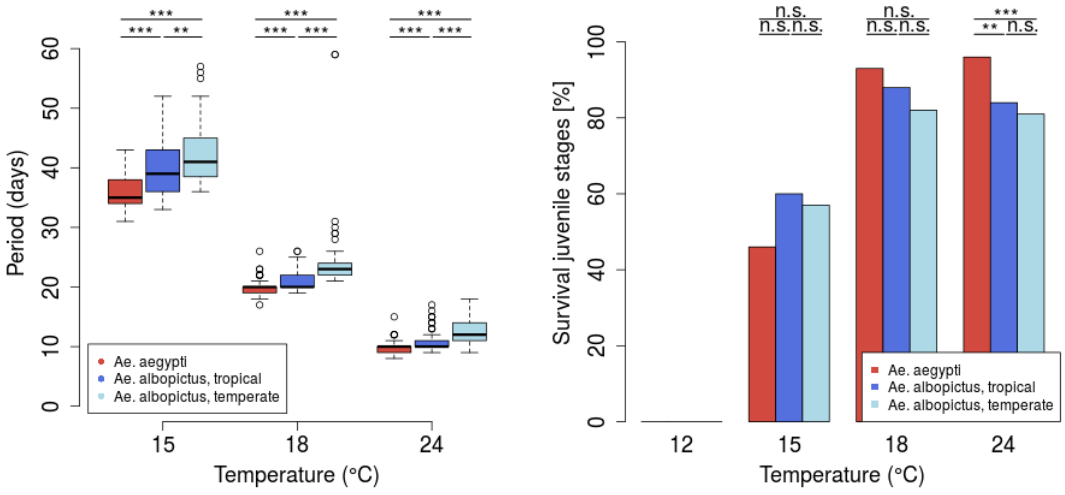

Figure 6.4: Juvenile stage Time and survival from hatching from the egg until eclosion to imago. Symbols over crossbars denote significance level: n.s.: not significant, *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$.

Pre-Blood Meal Period

We also measured the time until females took their first blood meal, see Figure 6.5. The data does not show a clear trend, probably because not many females fed at the lower temperatures. The fractions of females fed, though showing a somewhat clearer trend, should be handled with care as we experienced high mortalities of adult mosquitoes in some cages. Using Wilcoxon's test shows that the time to first blood meal for temperate and tropical strain only differs significantly at 24 °C.

Using Fisher's exact test to compare the numbers that fed between the temperate and tropical strain gives a significant difference at 18 °C ($N = 40$, $p = 0.03$) but not at other temperatures.

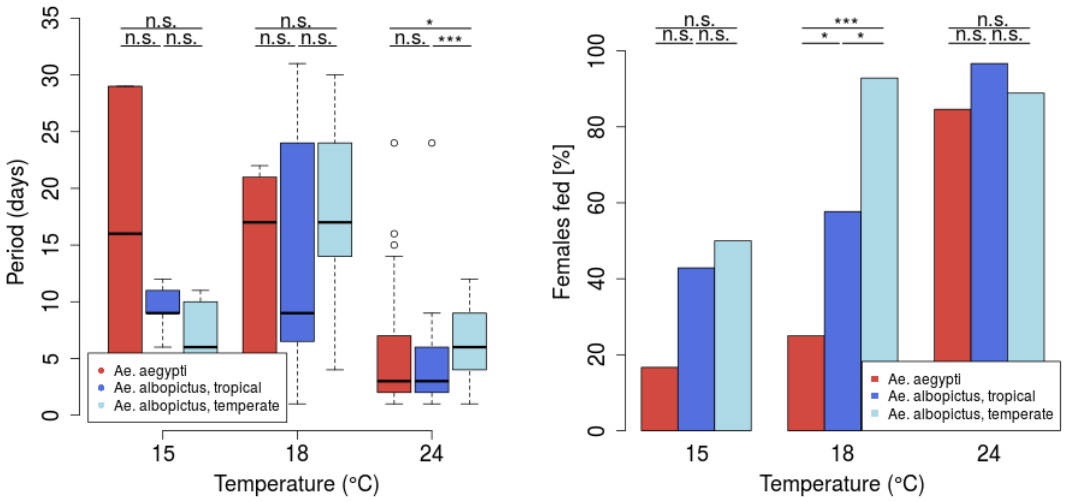

Figure 6.5: Pre-blood meal period Time to first blood meal and percent of females fed. Symbols over crossbars denote significance level: n.s.: not significant, *: $p < 0.05$, **: $p < 0.01$, ***: $p < 0.001$.

Both larval and pupal development times for both strains are well in the range of published literature, see Figure A6.2.

6.3.2 Tropical *Ae. aegypti*

To compare development and survival of *Ae. aegypti* to *Ae. albopictus*, we pooled the data of the two *Ae. albopictus* strains (not shown). *Ae. aegypti* shows significant faster larval development at all temperatures (Wilcoxon, all p-values < 0.001) and faster pupal development at 15 °C and 18 °C (Wilcoxon, both p-values < 0.001). The combined juvenile class of *Ae. aegypti* shows faster development compared to *Ae. albopictus* at all temperatures (Wilcoxon, all p-values < 0.001). Time to first blood meal was not statistically different.

Larval survival was only significantly higher at 24 °C, pupal (and combined pupal and larval) survival is lower at 15 °C, not significantly different at 18 °C, and higher at 24 °C (Fisher, $N = 300$,

$p = 0.049$, $p = 0.061$ and $p < 0.001$, resp.). Blood feeding rate was not significantly different except for 18 °C, where it was lower (Fisher, $p < 0.001$).

Again, larval and pupal development times and survival probabilities are well in the range of the published literature, see Figure A6.1.

6.4 Discussion

We found no significant total survival difference between temperate and tropical *Ae. albopictus* strains. We thus find no statistical support for our hypothesis that temperate *Ae. albopictus* show higher survival probabilities in their larval or pupal stages as adaptation to colder climates. We did, however, find a slower development of the aquatic stages for the temperate strain. Though this was not expected, it might actually indicate an adaptation to colder temperatures; while the tropical *Ae. albopictus* strain showed similar development curves to the tropical *Ae. aegypti*, the temperate strain differed significantly.

These results are similar to the findings of Tsuda et al. (1994). They compared a *Ae. albopictus* strain from temperate to subtropical Japan with a strain from tropical Thailand at 27 °C. They also found longer development times for the aquatic stages of the Japanese strain, together with an increased blood meal uptake that resulted in a higher reproduction rate. The positive relationship between a slower larval development and a larger body size (Christiansen-Jucht et al., 2015), and an increase in oviposition rate (Yeap et al., 2013; Emami et al., 2013) and clutch size (Renshaw et al., 1994; Emami et al., 2013; Davis et al., 2016) with body size has been shown in several mosquito studies. Moreover, a slower development means that the mosquito spends more time in the aquatic stage with a slightly higher survival, compared to the adult stage (compare daily survival plots of Figure A2.2). The temperate strain could thus wait out colder periods in the more resilient aquatic stages. Unfortunately, we could not measure body size or fecundity of female mosquitoes in our experiments to directly show that the longer development periods lead to higher offspring numbers.

Climate projections suggest that cold spells will still occur in Europe with warming climates, even though with lower frequencies (Galli et al., 2010; Van Oldenborgh et al., 2015). *Ae. albopictus* strains from temperate regions will thus need to be able to withstand cold temperatures in their active stages, as it has already been shown for their egg stages (for strains from the US and Europe) (Hanson and Craig, 1995; Thomas et al., 2012).

Ae. aegypti showed much faster development rates compared to *Ae. albopictus* at all temperatures. Survival probabilities of both species are similar for temperatures above 10 °C, while other studies find higher mortality rates of *Ae. aegypti* larvae at temperatures below 10 °C (Chang et al., 2007). This raises the question why, when *Ae. aegypti* was present in Mediterranean Europe historically (Holstein, 1967; Schaffner and Mathis, 2014) and still is around the Black Sea (Kotsakiozi et al., 2018), and it is probably frequently imported to Europe (e.g. Scholte et al., 2010; Dallimore et al., 2017), is it not present in southern Europe as conditions get even more suitable?

Unfortunately, we could not directly control relative humidity (RH) and the photoperiod in the incubators. While each strain in the same incubator experienced the same conditions, the RH varied between incubators even though we kept a constant amount of water in each. A lower survival at lower RH has been found for adult *Ae. aegypti* in some studies (Mogi et al., 1996;

Canyon et al., 1999) but not in others (de Almeida Costa et al., 2010). The photoperiod has no effect on development time or survival though (Costanzo et al., 2015, 2016) and both species are often found in shaded breeding habitats (Tun-Lin et al., 1995; Unlu et al., 2013; Li et al., 2014), reflecting the indirect light in our incubators. By using eggs that were recently caught in the wild and only raised in the laboratory to the F3 generation for the experiment, we were able to exclude adaptation to laboratory conditions.

These findings are especially interesting for dynamical modelling studies that have so far relied on (sub-)tropical data only (e.g. Tran et al., 2013; Erguler et al., 2016). While it seems to be valid to use data from tropical strains to model population dynamics in temperate regions, future modelling studies could analyse the effect of different larval developments and subsequent varying body sizes on reproduction success in colder climates.

In conclusion, we find that temperate *Ae. albopictus* do not show a higher survival at low temperatures, instead they show a slower development than their tropical equivalent. This could help the mosquito to withstand harsh spring conditions in temperate zones.

Conclusion

To estimate the risk of invasive mosquito species establishing in the UK and subsequently transmitting diseases, it is important to understand how temperature and other environmental factors influence the mosquito's population and disease dynamics. This understanding enables scientists, public health officials and policy makers to make better predictions about mosquito occurrence and abundance, to give realistic risk estimates for disease transmission in temperate regions and should ultimately lead to appropriate surveillance and control policies.

Climate-driven models are the method of choice to analyse the effects of temperature, rainfall or photoperiod on mosquitoes. In a way, these mathematical models can be regarded as experiments looking for example at infection dynamics, that would otherwise not be ethically or financially feasible (Mansnerus, 2015). In this work we presented several modelling approaches to investigate how current and future climates are shaping the life cycle and disease transmission of *Ae. albopictus*, the mosquito currently spreading in Europe.

In chapter 2 we analysed the UK's suitability for *Ae. albopictus*. We found that for now, only some areas in south-east England seem to be suitable for a successful mosquito establishment. Future scenarios indicate, however, that the mosquito could become established over larger parts of the UK. The mosquito's spread in Europe was modelled in chapter 3 and looking at the UK suggested that it could spread over Southern England within 30 years following an introduction.

In chapter 4, we analysed population dynamics of *Ae. albopictus* and its role in dengue transmission in China, a country in which this species is long since established. We were able to realistically model China wide mosquito presence and infection dynamics during the dengue outbreak 2014 in Guangzhou. By applying these findings to the UK, we found that temperatures are not yet high enough to enable mosquito populations to build up to high numbers and effectively transmit arboviruses. Individual cases of disease transmission cannot be excluded though. Global Zika transmission risk was estimated in chapter 5, linking the 2015 outbreak in Brazil to the warm temperatures caused by the El Niño event that year. By applying the model specifically to temperate regions again, we found that southern Europe is suitable for chikungunya transmission and, to a lesser extent, for dengue, but not for an effective Zika transmission.

Finally, we conducted a laboratory experiment in chapter 6 to investigate if European *Ae. albopictus* show any adaptation to colder climates that would allow the mosquito to expand its range in Europe even further. We did find some differences in larval development compared to

its tropical strain that could actually act as a cold-adaptation mechanism, but the results are not clear.

In conclusion, we can answer the questions that we asked in the beginning: *Ae. albopictus* is already able to become established in some parts of south-east England and future climates will only lead to more suitable conditions in the UK. Possible mosquito numbers will be small though and climate conditions are not yet suitable for effective arbovirus transmission. There is, however, still a chance for individual cases of disease transmission in warmer summer months.

In the next sections, we will discuss some implication and limitations of the presented work.

Mosquito Surveillance and Control

To realistically estimate the risk of arbovirus transmissions, it is important to know the exact distribution of the vector species. *Ae. albopictus*' first successful introduction to Europe happened in 1975 or earlier, in Albania, but was only identified in 1979 (Adhami and Reiter, 1998). While a close surveillance and possible eradication after this identification was not realised, the vector was introduced from abroad again in 1990, this time to Italy (Sabatini et al., 1990). Its spread in Italy was more closely followed (Dalla Pozza et al., 1994; Romi et al., 1997, 1999; Romi, 2001; Peretti et al., 2009; Roiz et al., 2011). Unfortunately, surveillance and mitigation efforts did not stop its spread to neighbouring countries that in turn had to start their own surveillance programmes, see Table 7.1. VectorNet, a project by the European Centre for Disease Control and Prevention, ECDC, and the European Food Safety Authority, summarises the findings from the national surveillance programmes and other studies (ECDC Vectornet, 2019).

Both ECDC and the American CDC have both released guidelines on surveillance and control strategies (ECDC, 2012; USA CDC, 2017). Following these guidelines, countermeasures are initiated after detections in new regions to stop *Ae. albopictus* from establishing or spreading further (Romi et al., 1999; Wymann et al., 2008; Scholte et al., 2010; PHE, 2017). So far, insecticides spraying has been the method of choice, sometimes supported by breeding site treatment with *Bacillus thuringiensis* (Williams et al., 2014). But insecticide resistance of *Ae. albopictus* is a growing concern (Li et al., 2018). Alternative controls are in development but not fully ready for action, e.g. *Wolbachia*, genetically modified mosquitoes, spatial repellents and others (Roiz et al., 2018; Achee et al., 2019).

Using mathematical models to analyse the suitability for *Ae. albopictus* and its spread can help to identify regions with a high risk of mosquito introduction and establishment. Results of chapters 2 and 3 show for example, that a monitoring of SE England is important to stop the vector from successfully entering the UK. Though this mosquito's role in disease transmission might be limited in the UK for now (compare chapter 4), this might change in the future (Liu-Helmersson et al., 2016). Moreover, its monitoring and control are associated with huge costs when it has become established (Romi et al., 1999).

Table 7.1: Vector surveillance European countries with occasional or systematic mosquito surveys for *Ae. albopictus*. The mosquito has been introduced to all the listed countries, whether established or not.

Country	*Ae. albopictus* established	Start of surveillance	Reference
Albania	x		Adhami and Reiter (1998)
Austria		2017	Schoener et al. (2019)
Belgium		2013	Deblauwe et al. (2015)
Bulgaria	x		ECDC Vectornet (2019)
Bosnia & Herzegovina	x		ECDC Vectornet (2019)
Croatia	x	2016	Klobucar et al. (2006); Croatian Institute of Public Health (2018)
Czech Republic			Rudolf et al. (2018)
France	x	2005	EID (2016); Ministère des Solidarités et de la Santé (2019)
Germany	x	2012	Werner et al. (2012); Walther et al. (2017)
Greece	x	2010	Patsoula et al. (2017)
Italy	x	1990s	Sabatini et al. (1990); Romi et al. (1999)
Montenegro	x		ECDC Vectornet (2019)
Netherlands	x	2006	Scholte et al. (2010)
North Macedonia	x		ECDC Vectornet (2019)
Portugal		2008	Osório et al. (2014)
Romania	x		Prioteasa et al. (2015)
Russia	x		Akiner et al. (2016)
Slovenia	x		Kalan et al. (2017)
Spain	x		Aranda et al. (2006); Collantes et al. (2015)
Switzerland	x	2000	Flacio et al. (2015); Suter et al. (2016)
UK		2009	Vaux and Medlock (2015); PHE (2017)

In the future, environmental change, and a growing and more connected population will promote vector-borne disease risk further (Sutherst, 2004; Myers et al., 2013). In consequence, efforts to counterbalance these factors must include better surveillance systems of both vectors and viruses, a facilitated exchange of data gained across countries (VectorNet), and multidisciplinary infectious disease approaches that include epidemiologists, biologists, modellers and, last but not least, climate scientists.

Climate Change

The emergence and spread of mosquito-borne diseases are among the most likely things to change with climate change (Lafferty, 2009; IPCC, 2013). A recently published article by Ryan et al. (2019) received a lot of media attention. It suggests that an additional global population of about 500 million people will be at risk from mosquito-borne diseases linked to *Ae. albopictus* alone in 30 years time (under a moderate carbon emission scenario, RCP4.5). At current conditions, they estimate about 6.3 billion people at risk from diseases linked to *Ae. albopictus*, i.e. 84% of the global human population.[2] Though the authors make some very rough assumptions (e.g. they do not take the actual mosquito distribution into account) and the numbers will be a bit too high, they show the dimensions of this issue.

Europe, with a temperature increase of 2 to 4 °C by 2100 (Füssel et al., 2012), will notice this change particularly strong. Here, the largest increase in population at risk is projected

[2]For comparison, the WHO estimated that about half the global population is at risk from all VBD (malaria, Chagas, trypanosomiasis, dengue,...) combined (WHO, 2008).

(Ryan et al., 2019), mostly due to an increased suitability for vector species and their subsequent spread (Kraemer et al., 2019). Models show that southern UK will become more suitable for *Ae. albopictus* by 2030–2050 (Caminade et al., 2012) which is supported by our findings, compare section 2.3. In addition to an increased risk of local transmission in these temperate regions, the number of imported cases will also increase due to a higher number of arbovirus outbreaks globally (Medlock and Leach, 2015).

Climate change might also have some other, indirect effects on mosquito-borne diseases. Birds might return earlier to their breeding sites with warmer temperatures (Marra et al., 2005), potentially importing viruses like WNV earlier and prolonging the transmission season. Climate change might also facilitate host switching events of viruses, e.g. from invasive vectors like *Ae. albopictus* to endemic mosquito species in the UK (Hoberg and Brooks, 2015).

Climate-driven models can quantify these effects. These models can make short-term disease risk forecasts, using historical climate data and short-term weather forecasts, for example for dengue in Singapore (Hii et al., 2012) or Rift Valley fever in Kenya (Linthicum et al., 1999). They can also make long-term disease risk projections that require climate projections rather than historical climate data. General or regional circulation models simulate future temperatures, precipitation, or carbon cycles by calculating processes in the Earth's atmosphere and oceans. Fed through a the disease model, these climate projections can be used to provide probabilistic disease forecasts for decades ahead. Resulting risk scenarios often serve as a warning of the possible impacts of climate change.

Most studies agree that the costs to stop climate change will be lower than the costs caused by climate change (Nordhaus, 2010; Sterner, 2015). However, a lot of policy makers still approach climate change half-heartedly at most (e.g. CDU, 2017) as worldwide protests show. Campbell-Lendrum et al. (2015) conclude that the output of climate change and vector-borne disease research has to be targeted to policy makers more directly, by relating findings to present day health risk assessment and management. The WHO has published a plan to tackle the health impacts of climate change, whose points include 1) to strengthen international collaboration, 2) to raise awareness, 3) to promote scientific research and 4) to support the implementation into policies WHO (2015).

Limitations

While climate-driven models can help us to explain past events, warn us about present risks, and anticipate the probability of future outbreaks, there are some limitations especially to risk predictions. First of all, all models are only as good as the data that go into their development and validation and thus heavily rely on laboratory or field data. Intensive literature screens and meta-analyses are good ways to limit the effects of flawed data (see e.g. Brady et al., 2013; Eisen et al., 2014; Manore et al., 2014).

Second, models are only approximations of the real world and have to simplify or neglect cer-

tain factors. The models presented here focus mainly on climate factors and do not take into account behavioural adaptations of the population and health services, or socio-economic and subsequent medical improvements. As an example, the drop in malaria prevalence over the last century is not related to climatic factors but is primarily owing to the implementation of vector-control measures (Reiter, 2001, 2008). It is thus necessary to also consider socio-economic developments, once a geographical range for vector and disease is identified with climate models. A good example is the work by Perkins et al. (2016) that uses both climatic and economic drivers for a statistical model of the risk of Zika to child-bearing women. Wallace et al. (2018) show how socio-economic factors could be included in dynamic disease models with stochastic processes.

Other neglected environmental factors include the ongoing urbanisation process that is favourable especially for the domesticated *Aedes* species (Li et al., 2014), while wetland and environment shaping can create mosquito habitats for other species (Medlock and Vaux, 2015). Deforestation and land development in the tropics also lead to the introduction of diseases into new environments (Vasconcelos et al., 2001). Moreover, scientists and hobby entomologists have noticed an ongoing decline in general insect populations (but not mosquitoes), with about 75% less insect biomass in the air compared to 1990 (Hallmann et al., 2017; Vogel, 2017). As the amount of insects is directly linked to the number of birds, especially farmland birds, these have seen a steep decline too (Donald et al., 2001; Department for Environment, 2018). Without an effective top-down control of birds (Mäntylä et al., 2011), mosquito numbers could increase even further in the future.

Both vectors and viruses will experience mutations which could lead to an increase in transmission probability, as seen with chikungunya and *Ae. albopictus* (Tsetsarkin et al., 2007). Vectors could also adapt to colder temperatures, facilitating their spread in temperate climates, a process that could happen in as little as 7-10 years (Egizi et al., 2015). We tried to analyse the extent of *Ae. albopictus*' adaptation to European climates in our laboratory study but did not get clear results. However, we saw that the temperate strain already differed significantly from its tropical variant in its development rate. Including all these additional factors into a single model seems infeasible and impractical. Reviews and meta-analyses of specialised models can help to see the larger picture (e.g. Tjaden et al., 2018).

Another limitation of dynamical modelling concerns their structure. The used models and the vast majority of discussed dynamical models are deterministic, yielding the same results for the same inputs. But nature is more complex, realistic mortality and development rates, transmission probabilities and EIPs cannot described by a single value or a curve, they all show fluctuations and variance depending on individual mosquitoes, locations, microclimates etc. (compare Lee, 1994; Delatte et al., 2009; Westbrook et al., 2010, for just a few examples on the ranges of mosquito development). Other approaches could make use of stochastic effects or probability theory to assign parameters to a distribution on ranges or families of curves. This would reflect the uncertainty with climate-driven models more realistically. At least, most problems are analysed with a range of models that all make different assumptions that can be

compared and if possible combined with different climate scenarios, to have an estimate of the uncertainty that naturally comes with model predictions (Caminade et al., 2014).

Another method to estimate model parameters and their uncertainties is to directly use observation data. Instead of deriving parameters from published data and meta analyses, the model is repeatedly run with a range of parameters to minimise the outputs difference to observation data. Erguler et al. (2016) use this method to update their a priori winter mortality parameter with posterior estimates. Software packages are available for parameter and uncertainty estimations from observation data (Kaschek et al., 2019).

One last point should be made concerning the general limitations of modelling studies. While it is common practice to specify all model settings and parameters, the complete reproducibility of most model outputs is still difficult. Challenges can be unavailable code, missing or insufficient documentation and still incomplete parameter specifications. However, there is now a strong incentive or even a requirement to make computer code publicly available with publication and best practise instructions can help to write clear, understandable code for other researcher to test and build on (Wilson et al., 2014, 2017).

Outlook

The risk of mosquito-borne disease transmission depends on four factors and each of them can be the target of future work:

1. Host susceptibility. While the susceptibility for an emerging disease is naturally high in the naïve populations of Europe, future work could also look at the impact of vector-host interaction frequencies, disease awareness and other social factors that could de- or increase the risk of a pathogen transmission to the host (e.g. Omodior et al., 2018).

2. Vector presence and competence. While *Ae. aegypti* and *Ae. albopictus* are relatively well studied (compare appendix A2.1 and A5.2), temperate mosquitoes and their vector competence are critically understudied (see Blagrove, 2016; Gutiérrez-López et al., 2019, for exceptions). To better estimate disease transmission risk in Europe and the UK in particular, laboratory and field studies should include endemic mosquito species too. Additional studies could then analyse adaptations of invasive vector species to temperate climates. For example, our laboratory experiment from chapter 6 could be followed up to check if the longer duration of the larval stage of temperate *Ae. albopictus* is actually an adaptation to colder climates and how it impacts on the mosquito's possible expansion in Europe.

3. Pathogen presence. After the introduction and spread of *Ae. albopictus*, Italy had a susceptible population, a competent vector and annually suitable climate conditions for arbovirus transmission, compare section 5.3.2. However, there have only been two arbovirus outbreaks with a couple of hundred cases since 2007, probably because the virus importation frequency by infected travellers was relatively low. To get a better understanding of pathogen introductions to non-endemic regions, flight network models could

analyse the disease importation risk for passengers (Gardner and Sarkar, 2013; Walters et al., 2018) and field studies could investigate zoonotic disease and (tick) vector introductions by migrating birds (Rappole et al., 2000; Jameson et al., 2012) or other live animal trade (Durand et al., 2013).

4. Environmental conditions. This is quite a wide area that also includes climate conditions. Numerous climate-driven models are available to estimate disease transmission risk. However, the vast majority of them use standard approaches such as ODEs and averaged climate data as model drivers which could be modelled more realistically. Future work could for example combine effect of the diurnal temperature range, DTR, on disease transmission with stochastic differential equations or DDE models, compare chapters 2 and 4. Other work on environmental factors could focus on spatial vector distribution in regard to micro-climates, e.g. in cities, and land use (Zahouli et al., 2017; Yamashita et al., 2018).

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Data Accessibility

The E-OBS climate data set for Europe is publicly available, following registration, at https://www.ecad.eu/download/ensembles/ensembles.php. The UKCP09 climate data set for the UK is available, following registration, at https://www.metoffice.gov.uk/climatechange/science/monitoring/ukcp09/download/index.html. The ERG5 Eraclito climate data set for the Emilia-Romagna region is publicly available at https://www.arpae.it/dettaglio_documento.asp?id=6147&idlivello=1528. The climate projections of the NASA NEX-GDDP project are available, following registration, at https://cds.nccs.nasa.gov/nex-gddp/. Population density data from GPWv4 is publicly available, following registration, at http://sedac.ciesin.columbia.edu/data/collection/gpw-v4. Model scripts are available in the ESM. The global monthly temperature and precipitation data sets GHCN CAMS aand GPCC are publicly available at https://www.esrl.noaa.gov/psd/data/gridded/data.ghcncams.html and https://www.esrl.noaa.gov/psd/data/gridded/data.gpcc.html. The APHRODITE climate data sets for Asia are available, following registration, at https://climatedataguide.ucar.edu/climate-data. The CMCD climate data set for China is available at https://data.cma.cn/en. *Ae. albopictus* container index data for the Emilia-Romagna region is publicly available at http://www.zanzaratigreonline.it/.

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Appendix

A2.1 ODE Model Parametrisation

Development and fecundity rates

According to Quinn (2017), development rates do not continuously increase with increasing temperature but show an optimum after which they decrease again. We thus choose a quadratic polynomial function $d(T) = a \cdot T^2 + b \cdot T + c$ for development periods as shown in Figure A2.1, and took the inverse to get development rates, $\delta(T) = 1/d(T)$. Data for egg development did not show a clear relationship with temperature, so we chose the median of all data points as a constant.

Egg laying rates were averaged over the whole lifetime of a mature female, excluding the first pre-bloodmeal period. A skewed Gaussian distribution was fitted to the data.

Survival rates

As the daily mortality is rarely given in the literature, we have to estimate it from the mean development time t_{dev} and the fraction of absolute survival of the larval/juvenile stage, S. For a stage X, we assume exponential mortality:

$$\tfrac{d}{dt} X(t) = -\mu\, X(t),$$

with some mortality rate μ. We further assume that S is reached after the mean development time t_{dev} and can thus estimate μ by

$$\begin{aligned} \mu &= -\frac{1}{t_{\text{dev}}} \ln\left(\frac{X(t_{\text{dev}})}{X(0)}\right) \\ &\approx -\frac{1}{t_{\text{dev}}} \ln(S). \end{aligned}$$

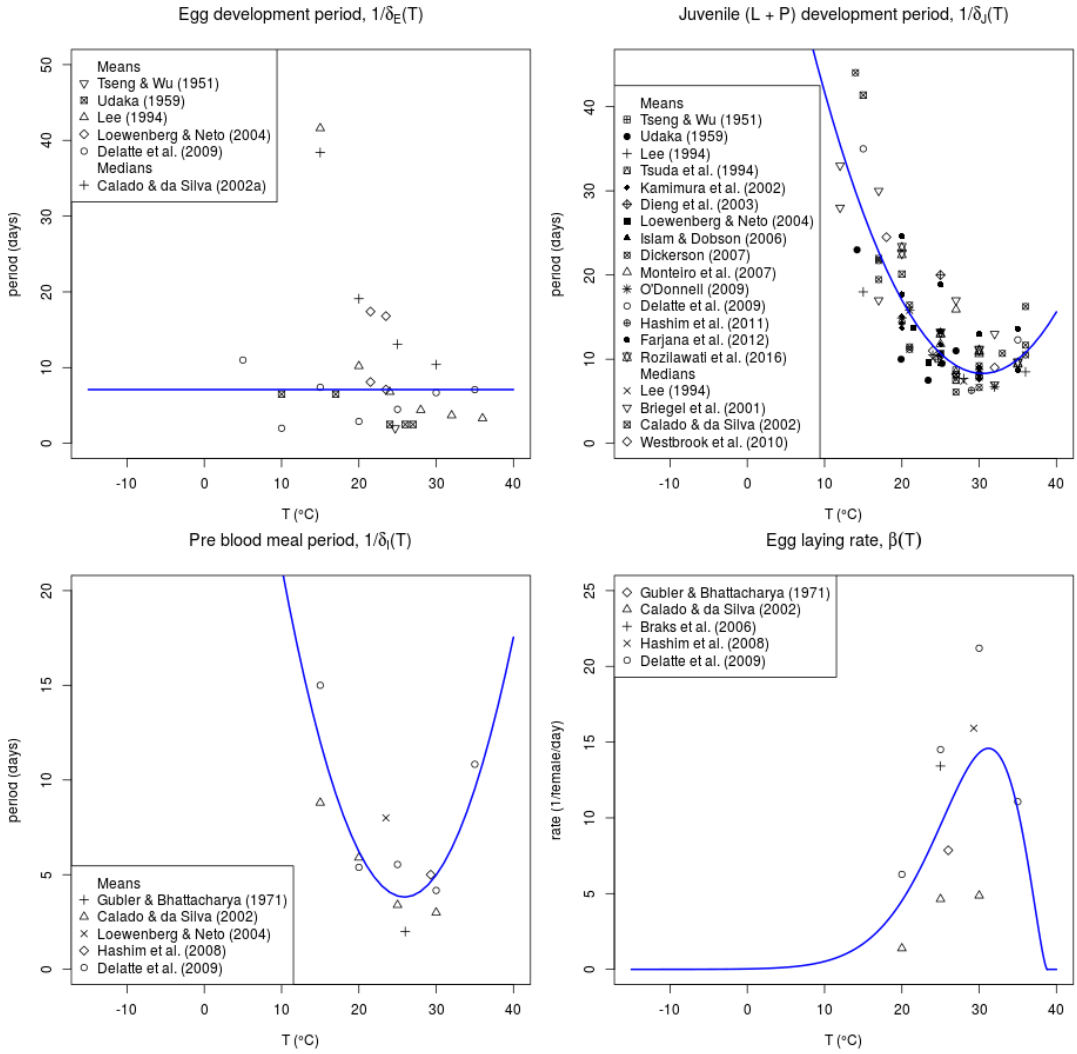

Figure A2.1: Development periods for *Ae. albopictus* eggs, juveniles, and immature females. Egg development did not show a clear correlation with temperature, so we chose a constant period. Bottom right: female fecundity given by eggs per mature female per day.

The daily survival rate follows by

$$\begin{aligned} s &= \frac{X(1)}{X(0)} \\ &= e^{-\mu \cdot 1} \\ &= e^{\frac{1}{t_{\text{dev}}} \ln(S)} \\ &= S^{\frac{1}{t_{\text{dev}}}}. \end{aligned}$$

Fitting functions to daily survival rates were of the form $s(T) = a \cdot \exp(-(\frac{T-b}{c})^6)$ (Figure A2.2). We use a sextic rather than a quadratic exponent as data suggest an optimal plateau rather than a peak around an optimal temperature. The daily survival probabilities are subsequently translated into mortality rates suitable for a differential equations setting by taking the negative natural logarithm, $\mu(T) = -\ln(s(T))$.

Note that this is simply reversing the last step of the daily mortality rate calculation. We only plot the daily rate instead of μ, as it is easier to interpret.

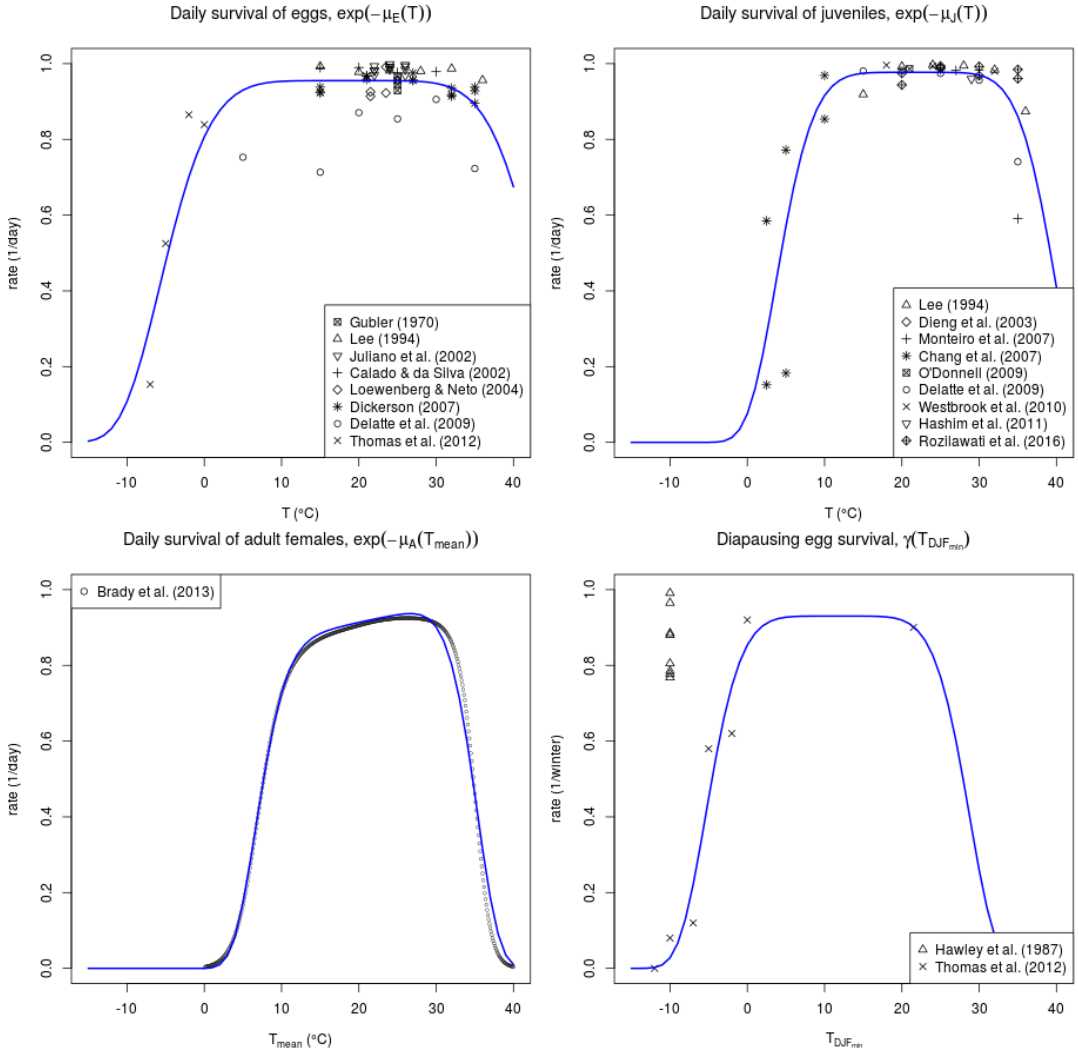

Figure A2.2: Daily survival rates for summer eggs, juveniles, and adults and winter survival probability for diapausing eggs. Data points from Chang et al. (2007) are only for L1 and L4 larvae. On the x-axis is either the diurnal oscillating temperature T, daily mean temperature T_{mean}, or the minimum winter temperature of December, January and February, $T_{\text{DJF, min}}$.

For daily survival of adult mosquitoes, we only use the meta analysis of Brady et al. (2013) as they investigate survival in the field which we are interested in. The field survival rates are calculated for daily or even monthly mean temperatures (Bonnet and Worcester, 1946; Takagi et al., 1995; Maciel-de Freitas et al., 2006; Lacroix et al., 2009; Marini et al., 2010), so we decided to use daily mean temperatures to calculate adult mortality rates, rather than the full diurnal temperature cycle. We used a temperature-dependent factor of $T^{0.1}$ to account for the skewness in the daily survival probability, $\mu_A(T) = -\ln(s_A(T) \cdot T^{0.1})$.

Finding a temperature-dependent curve for diapausing egg survival was the most challenging task as there are no laboratory studies investigating the survival at constant temperatures for periods of up to five months. However, some studies analyse the effect of sub-zero treatments on the eggs' survival rates (Hawley et al., 1987; Thomas et al., 2012; Kreß et al., 2017). They suggest that hatching success does not change significantly after a 24h exposure to -2 °C in the F1 generation (Kreß et al., 2017) and another study found the length of the egg maturation period does not greatly effect survival rates (Gubler, 1970). We thus make the assumption that only the absolute minimum temperature experienced throughout the winter is shaping the survival curve. This survival probability is then applied only when eggs are hatching in spring. This is in line with the findings of Erguler et al. (2016) whose fitted daily winter mortality was too high to give meaningful results. In the end, we used a curve fitted to survival data of Italian eggs against minimum temperatures (Thomas et al., 2012) (Figure A2.2).

We assume that any remaining diapausing eggs that have not hatched until August are non-viable, as temperatures have not reached 11 °C in mid-summer, and remove them. It has been shown though, that *Ae. aegypti* eggs can survive 365 days in their desiccated stage (Faull and Williams, 2015), but this was only for laboratory conditions at temperatures above 17 °C.

There are some studies looking into the interaction of temperature and larval densities on mortality of *Aedes* mosquitoes but they do not show a clear pattern (Hapairai et al., 2014). We thus keep temperature-related and density-related mortalities separated.

Diapause

The relationship between latitude, L, and the critical photo period $\mathrm{CPP_A}$ after which half of the eggs laid go into a diapausing state shows a positive correlation (Urbanski et al., 2012). We use the observations made in Japan and in the US after adaptation to derive a linear function for our model, see Figure A2.3.

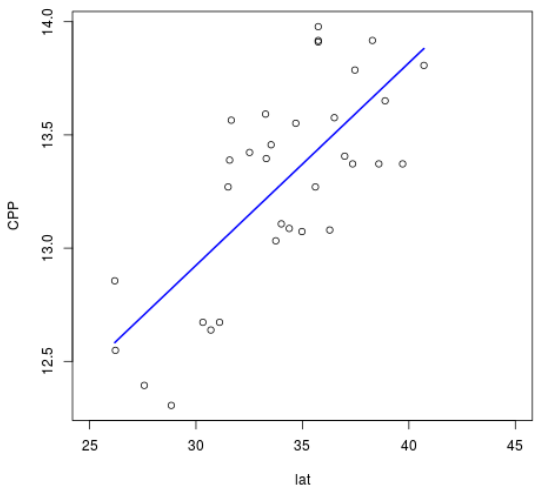

Figure A2.3: Relationship between latitude, L, and the critical photo period $\mathrm{CPP_A}$ in Japan and the US after adaptation (Urbanski et al., 2012).

The hatching of diapausing eggs in spring is triggered by a critical temperature, $\mathrm{CTT_S} = 11\,^{\circ}\mathrm{C}$ and photo period, $\mathrm{CPP_S} = 11.25$ hours (Toma et al., 2003). Eggs then only hatch if mean temperatures over a period of 7 days reach this threshold (Jia et al., 2016).

A2.2 ODE Model with 7 Stages

Other studies use larvae and pupae instead of juveniles to model immature development, some studies also use host-seeking and gestating stages to model the gonotrophic cycle (Erickson et al., 2010; Tran et al., 2013; Jia et al., 2016), see Figure A2.4. An advantage of additional stages is that the development rate from egg to adult can approximate a Gamma distribution, which is more realistic with delayed development (linear chain trick) (Smith, 2011).

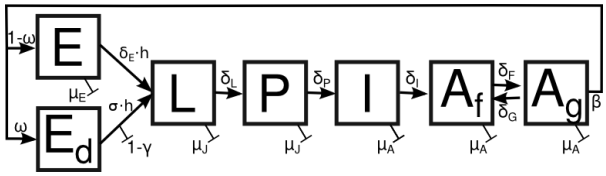

Figure A2.4: Model with juvenile class split up into a larva and a pupal class, and the mature female class split up into a host-seeking and a gestating/ovipositing class.

We tested whether such an extended model structure with additional parameters (Figure A2.5) improved the fit to observed container index (CI) data but it gave very similar results. Comparing model output with spatial observations failed to predict occurrences in parts of East Europe and north of 45°N. We thus chose the model with only five equations, as there is also more literature data available to parametrise the reduced model.

A2.3 ODE Model Step Size

For large maps, that are converted into large matrices, we often use a coarser step size of $\Delta t = 0.1$ to keep the computation time low. A coarser step size, however, goes along with greater numerical error, especially for explicit methods with a fixed step size such as forward Euler but also the more precise Runge-Kutta 4. This can for example lead to small negative values when mosquito numbers are rapidly declining, such as in autumn. We thus use a trick to avoid negative numbers: whenever we calculate negative values in a time step i, we recalculate this time step using a log transformation of our equation system:

$$\tilde{X} = \ln(X).$$

This has the advantage that the log-space is unconstrained, i.e. $D = (-\infty, \infty)$, and a re-transformation using the exponential function will always yield positive numbers.
Looking at a differential equation

$$\tfrac{d}{dt} X(t) = f(X(t))$$

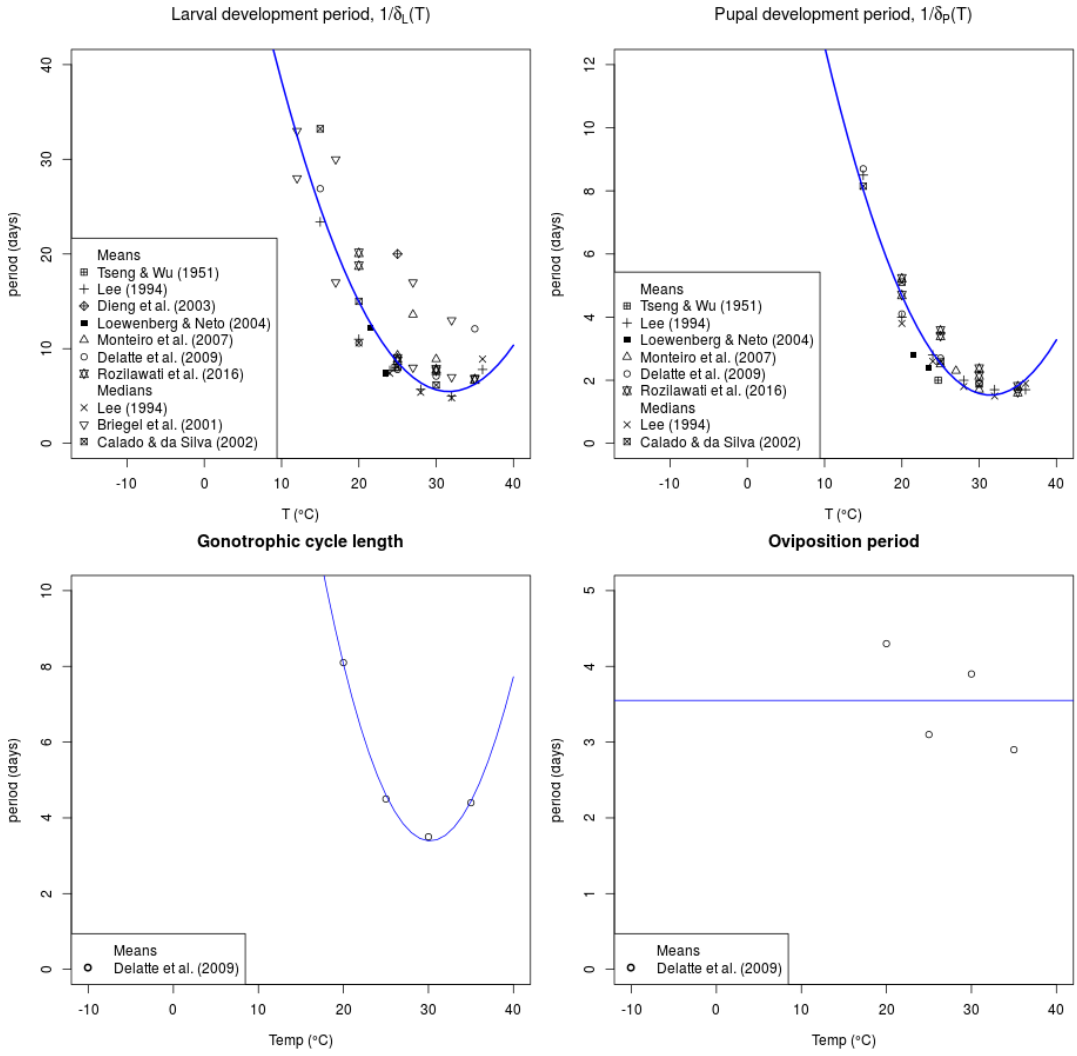

Figure A2.5: Development periods for larvae and pupae, as well as period from blood meal intake until oviposition (GTC) and period of oviposition. These are only used in the extended model with seven equations.

with f being a functional term, we get

$$\begin{aligned}\frac{d}{dt}\tilde{X}(t) &= \frac{d}{dt}\ln(X(t)) \\ &= \frac{1}{X(t)}\frac{d}{dt}X(t) \\ &= \frac{1}{X(t)}f(X(t))\end{aligned}$$

With the log-transformed variables, we thus have to solve the ODE system

$$\begin{aligned}
\tfrac{d}{dt}\tilde{E}(t) &= \beta\,(1-\omega)\,\frac{A(t)}{E(t)} - h\,\delta_{\mathrm{E}} - \mu_{\mathrm{E}} \\
\tfrac{d}{dt}\tilde{J}(t) &= h\,\delta_{\mathrm{E}}\,\frac{E(t)}{J(t)} + h\,\sigma\,\gamma\,\frac{E_{\mathrm{d}}}{J(t)} - \delta_{\mathrm{J}} - \mu_{\mathrm{J}} - \frac{J(t)}{K} \\
\tfrac{d}{dt}\tilde{I}(t) &= \tfrac{1}{2}\,\delta_{\mathrm{J}}\,\frac{J(t)}{I(t)} - \delta_{\mathrm{I}} - \mu_{\mathrm{A}} \\
\tfrac{d}{dt}\tilde{A}(t) &= \delta_{\mathrm{I}}\,\frac{I(t)}{A(t)} - \mu_{\mathrm{A}} \\
\tfrac{d}{dt}\tilde{E}_{\mathrm{d}}(t) &= \beta\,\omega\,\frac{A(t)}{E_{\mathrm{d}}(t)} - h\,\sigma
\end{aligned}$$

After computing the log-transformed variables for time step i we re-transform the variables with the exponential function and yield positive numbers.

We did not work with an entirely log-transformed system as numbers can get very small and are rounded to $-\infty$ eventually, which makes further computation very complicated.

A2.4 Suitability Index

We define the suitability of a certain year and location as the number of diapausing eggs at the end of the year divided by the (small) number of diapausing eggs at the beginning of the year, $E_i = E_d(x = 365)/E_d(x = 1)$. In our model, diapausing eggs do not experience a daily mortality (a survival probability is applied in spring instead, see A2.1) and thus accumulate over autumn. At the end of December, when almost all adult females have died off and no more eggs are produced, diapausing egg numbers E_d have reached a stable plateau and $E_d(x = 365)$ can be used for E_0 calculation without taking an average over a certain period.

It would be also possible to use other stages for comparison, e.g. the number of adult females during the summer. It would be necessary though, to use an average over a certain time period for this variant, as numbers of juvenile or adults can fluctuate on a daily basis. As an example, we define

$$A_i = \frac{\frac{1}{30}\sum_{x=201}^{230} A_i(x)}{\frac{1}{30}\sum_{x=201}^{230} A_{i-1}(x)}$$

as the averaged number of females over 30 days in July/August of one year divided by the averaged number of females over the same period in the previous year. Figure A2.6 shows mosquito development when introducing diapausing eggs at DOY = 1 and running simulations for 2016 (left) to calculate E_0, and mosquito development when introducing adult females at DOY = 200 and running simulations for 2015 and 2016 (right) to calculate A_0.

Resulting values for $E_0 = E_{2016}$ and $A_0 = A_{2016}$ are very similar, compare Table A2.1. Values for A_0 are slightly higher as relatively more females had been introduced than diapausing eggs.

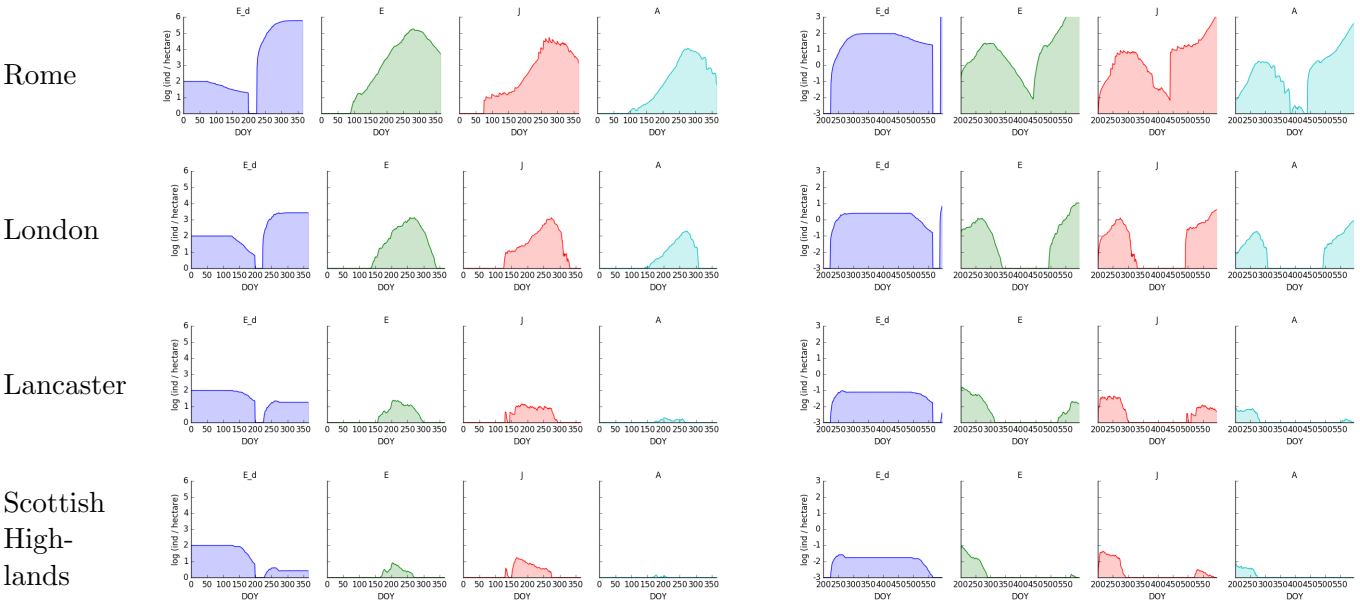

Figure A2.6: Mosquito population development Left plots show an introduction of $1 \cdot 10^2$ eggs per hectare at DOY = 1 for four locations, running the simulations for 365 days. E_i is then calculated by dividing the last time point of E_d by the first. Right plots show an introduction of $1 \cdot 10^{-2}$ females per hectare at DOY = 200 for the same locations, running the simulations for $2 \times 365 = 730$ days. A_i is then calculated by dividing the average of A for days 565 to 585 (days 200 to 230 of year 2), by the average of A for days 200 to 230 (of year 1). Please note the log-scale on the y-axis: When we remove diapausing eggs at DOY 200, we actually only remove a couple of eggs.

Table A2.1: Comparison of E_0 and A_0

Location	E_0	A_0	**Suitability**
Rome	6053.7	10243.8	Very suitable
London	27.3	32.7	Slightly suitable
Lancaster	0.18	0.23	Slightly unsuitable
Scottish Highlands	0.026	0.034	Very unsuitable

The suitability definition based on diapausing eggs has the advantage that simulations only have to be run with single calendar years (often easier with climate data sets) and that population numbers do not have to be averaged over long time periods and will thus use E_0 instead of A_0.

The definition of E_0 as the geometric mean of all E_i analysed has another advantage; $E_0^n = \Pi_{i=1}^n E_i$ gives an approximate value of population increase/decrease after n years; as an example let $E_1 = 3$, $E_2 = 0.5$ and $E_3 = 1.5$, then $E_0 = 1.3$ and thus slightly suitable, and $E_0^3 = 2.25$. Starting with one diapausing egg at the beginning of year 1, we can expect approximately 2.25 eggs at the end of year 3. This estimate does only hold in the first few years though, later on the mosquito population will approximate its carrying capacity and yearly egg numbers will more or less stagnate.

A limitation to E_0 is that it depends on the underlying population model. If the model does not correctly reproduce the climatic dependencies of the mosquito development and reproduction, the number of eggs at the end of the year will not be realistic, and neither will E_0.

A2.5 Climate Projections

The NASA-NEX GDDP project provides calibrated general circulation model (GCM) outputs (daily rainfall and temperature) for future emission scenarios (RCPs) and for historical experiments. 21 GCMs are available (https://nex.nasa.gov/nex/projects/1356/) at a spatial resolution of 0.25° (approximately $25\,km \times 25\,km$).

As the dynamical life cycle model for *Ae. albopictus* is computationally expensive to run, we took a subset of five GCMs out of 21, while keeping those models that represent the variability in the ensemble, i.e. GCMs that maximize uncertainty. For this, we first calculated land annual temperature indices for all GCMs and each emission scenario. We then kept the GCMs that were closest to the minimum, 25th percentile, median, 75th percentile and maximum temperature increase in the ensemble of the 21 GCMs (using the RMSE that minimized the distance to each categories, Table A2.2). Please see Jones et al. (2019) for full details.

Table A2.2: General circulation model and RMSE to closest category (min, 25^{th}, 50^{th}, 75^{th}, max temperature increase). Calculation of RMSE was done by Cyril Caminade.

	RCP4.5	**RMSE**	**RCP8.5**	**RMSE**
Minimum	inmcm4	0.485	inmcm4	0.512
25^{th} quantile	MRI-CGCM3	0.347	CESM1-BGC	0.360
Median	NorESM1-M	0.366	NorESM1-M	0.336
75^{th} quantile	CanESM2	0.333	CanESM2	0.326
Maximum	MIROC-ESM-CHEM	0.630	MIROC-ESM-CHEM	0.567

Before running the model for the climate projections, we plotted key climate factors for Western Europe: annual mean temperature, Figure A2.7 and annual rainfall amount, Figure A2.8. Plots are shown for the RCP8.5 emission scenario using the median warming model NorESM1-M.

We also analysed if climate models predict a change for the future DTR, or if the variance in annual rainfall is going to change. Concerning the DTR, studies have shown that the global warming in recent decades went along with a decrease in DTR (Easterling et al., 1997; Vose et al., 2005; Qu et al., 2014). Looking at London, Figure A2.9 (left) shows that the amplitude of the DTR is comparable to current conditions throughout the year, only showing a lower variability. The variance in annual rainfall is also very similar to current conditions for all five climate model projections, see Figure A2.9 (right). A change in annual rainfall variance could for example indicate an increase in heavy rainfall events and subsequent floods. This is also important for the DTR, as rainfall is negatively correlated with the DTR (Dai et al., 1999; He et al., 2015).

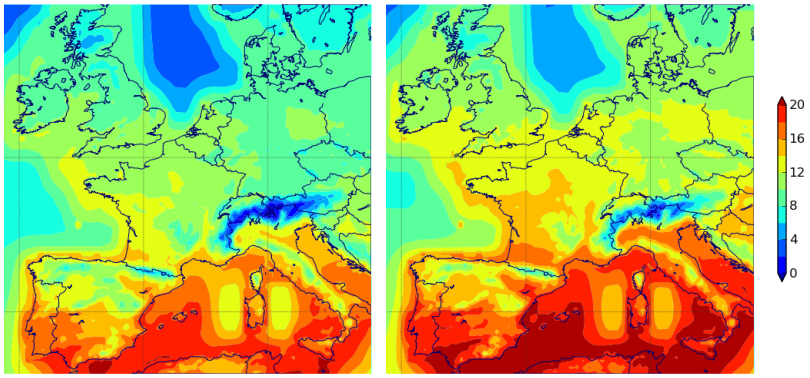

Figure A2.7: Annual mean temperature. The UK will experience a warming of about 2 °C in 50 years time in the RCP8.5 emission scenario.

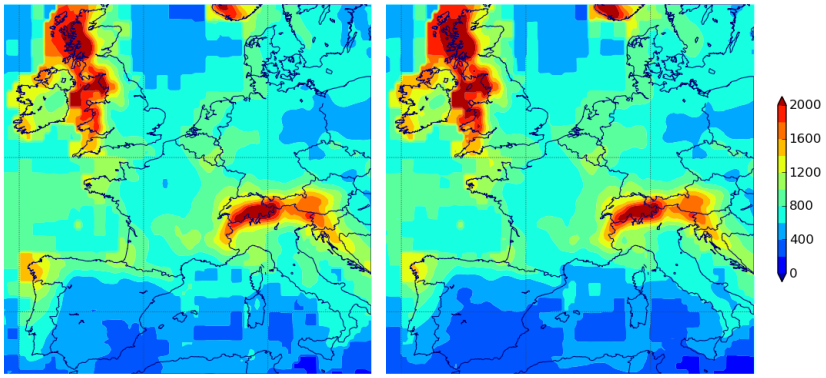

Figure A2.8: Annual precipitation. For the UK, the amount of rainfall per year will not change much in the future, the west coast might get a bit wetter as it already is.

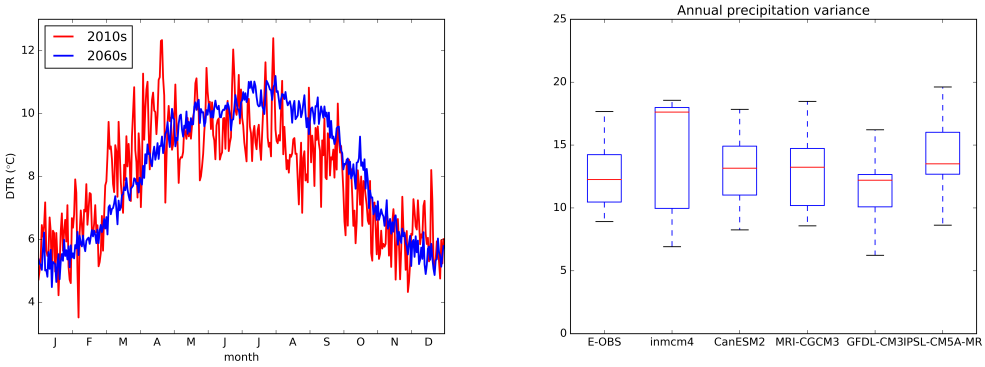

Figure A2.9: Future climate characteristics Right: The DTR in 50 years time shows a very similar amplitude for climate projections, even though it does not oscillate as strongly compared to the recent DTR. Left: Annual rainfall variance across present day climate data (E-OBS) and future climate projections (all others). The E-OBS climate data set and NEX-NASA climate projections for RCP4.5 have been used, with London as reference location.

A2.6 ODE Equilibria & Stability

We analysed the system of differential equations for equilibria and their according stabilities assuming a constant environment, i.e. no seasonal temperature and rainfall cycles, and rainfall positive. We get a trivial equilibrium, $(E^*, J^*, I^*, A^*, E_d^*) = 0$, and a non-trivial equilibrium:

$$
\begin{aligned}
A^* &= K\left(\left(h\,\delta_E\,\frac{\beta\,(1-\omega)}{\mu_e + h\,\delta_E} + \gamma\,\beta\,\omega\right)B - \delta_J - \mu_J\right)B \\
E^* &= \frac{\beta\,(1-\omega)}{\mu_E + h\,\delta_E}A^* \\
J^* &= \frac{1}{B}A^* \\
I^* &= \frac{\mu_A}{\delta_I}A^* \\
E_d^* &= \frac{\beta\,\omega}{h\,\sigma}A^*
\end{aligned}
$$

with $B = \frac{\delta_J\,\delta_I}{2\,\mu_A\,(\mu_A+\delta_I)}$.

Checking the eigenvalues of the Jacobian shows that the trivial equilibrium is unstable between 13 °C and 32 °C, meaning that we have a positive equilibrium in this temperature range for any positive carrying capacity K. K is non-zero if rainfall or the human population density are non-zero. The optimum temperature that maximises population numbers is at 27 °C, close to what Brady et al. (2013) have found for a maximum adult life span.

To analyse equilibria and stability with (regularly oscillating) seasonal climates, Floquet theory could be used (Klausmeier, 2008). While it cannot give analytical solutions for realistically fluctuating environmental conditions, it circumvents the problem of mosquitoes existing at unrealistically low numbers Mollison (1991).

A3.1 Mathematical Background of PDEs

The given system of (partial) differential equations can be rewritten as a single, vector-valued equation:

$$\partial_t v(x,t) = D\Delta v(x,t) + f(v(x,t))$$

with $v(x,t)$ denoting a vector containing each mosquito stage and being dependent on space x and time t,

$$v(x,t) = \begin{pmatrix} E(x,t) \\ J(x,t) \\ I(x,t) \\ A(x,t) \\ E_d(x,t) \end{pmatrix}.$$

We sometimes neglect arguments of variables to improve the readability, $v(x,t) \to v$. D is a diffusion vector with zero entries except for the mature female column, A, and f is the functional term representing all transitions between the mosquito stages,

$$f(v) = \begin{pmatrix} \beta\,(1-\omega)\,A - h\,\delta_{\mathrm{E}}\,E - \mu_{\mathrm{E}}\,E \\ h\,\delta_{\mathrm{E}}\,E + h\,\sigma\,\gamma\,E_{\mathrm{d}} - \delta_{\mathrm{J}}\,J - \mu_{\mathrm{J}}\,J - \frac{J^2}{K} \\ \frac{1}{2}\,\delta_{\mathrm{J}}\,J - \delta_{\mathrm{I}}\,I - \mu_{\mathrm{A}}\,I \\ \delta_{\mathrm{I}}\,I - \mu_{\mathrm{A}}\,A \\ \beta\,\omega\,A - h\,\sigma\,E_{\mathrm{d}} \end{pmatrix}.$$

In our two-dimensional case x is also a two-dimension vector, $x = \binom{x_1}{x_2}$, with x_1 and x_2 denoting the east-west and north-south direction on our given grid. The area we are looking at is called the domain and denoted by Ω and the domains boundary, the areas edge is denoted by $\partial\Omega$. We will assume zero-flux boundary conditions, i.e. individuals do not leave the area we are looking at, to exclude migration.

Together with an initial time conditions, these assumptions lead to an initial value problem of

$$\begin{cases} \partial_t v = D\Delta v + f(v) & on\ \Omega \\ \nabla \cdot \nu = 0 & on\ \partial\Omega \\ v(x,0) = v_0(x) & on\ \{t=0\}, \end{cases}$$

with the second equation describing the zero-flux boundary condition with ν normal to the

boundary. The initial time condition could be

$$v(x,0) = v_0(x) = \begin{pmatrix} E_0(x) \\ J_0(x) \\ I_0(x) \\ A_0(x) \\ E_{d_0}(x) \end{pmatrix} = \begin{pmatrix} 0 \\ 0 \\ 0 \\ 0 \\ 1 \end{pmatrix}$$

to start simulations with one diapausing egg per hectare, or $v_i(x,0) = v_{i-1}(x,365)$ to start simulations for year i with the last numbers of the previous year.

A3.1.1 Numerics

We used the finite volume method (FVM) to numerically evaluate the initial value problem (Knaber and Angermann, 2000). In FVM, the area of interest is divided into small volumes (the grid cells) and the in- and outflow of these cells is calculated (here: the movement of adult females across locations due to the diffusion process). FVM has the advantage that it is conservative, i.e. no individual mosquitoes get lost during the diffusion process. In contrast, the often used finite difference method which is not looking at grid cells but the grid points, might be compromised by truncation errors (Knaber and Angermann, 2000).

To solve certain partial differential equations, explicit numerical methods have to fulfil a criterion known as the Courant–Friedrichs–Lewy (CFL) condition (Courant et al., 1928). Simplified, it says that the length of the time steps (Δt) must but less than the time needed for an individual to move from one grid point to another. If the CFL condition is not met, the numerical evaluation can give false results. In our two-dimensional case, the time steps have to be chosen according to

$$\Delta t \leq \frac{\Delta x_1 \Delta x_2}{\max(D(x))}$$

with Δx_1 and Δx_2 being the time steps in east-west and north-south direction on our 25 km × 25 km grid. Implicit methods that evaluate the derivative at the proximate time step can be used to avoid this constraint but are difficult to implement when the functional terms (everything on the right hand side of the equation system except for the diffusion term) are non-linear. The IMEX methods circumvents this issue in that the functional term is evaluated explicitly at time point t, while the diffusion term is evaluated implicitly at the proximate time step $t + \Delta t$:

$$\partial_t v(x,t) = \partial_{xx} v(x, t + \Delta t) + f(v(x,t)).$$

Due to the high resolution of the climate data and the resulting large matrices, we choose spatial step sizes of $\Delta x_1 = \Delta x_2 = 1$ in order not to increase the computation time further. With $D < 1$ for a constant or time-dependent diffusion coefficient, it is possible to choose any time step $\Delta t < 1$ to fulfil the CFL conditions. However, we get $\max(D(x)) = 3.58$ for the location-dependent diffusion coefficient, so that approximately $\Delta t < 0.25$ fulfils the condition. As we were using $0.01 \leq \Delta t \leq 0.1$, we could have actually abandoned the IMEX method and

evaluated the diffusion term explicitly too.

A3.2 Climate Projection vs. Observations

All models of NASA's NEX-GDDP climate projection project were run for the period from 2006 to 2099, their onset is thus 12 years in the past. Inevitably, the projections will differ from the recordings of the past years and some models actually show a dip in annual temperatures for the recent years. We thus have to make sure that the projected temperatures are in the range of the actual recordings for the simulation of *Ae. albopictus* in future UK climates. Figure A3.1 shows that the temperatures of the recent three years are accurately predicted by the NorESM1-M model.

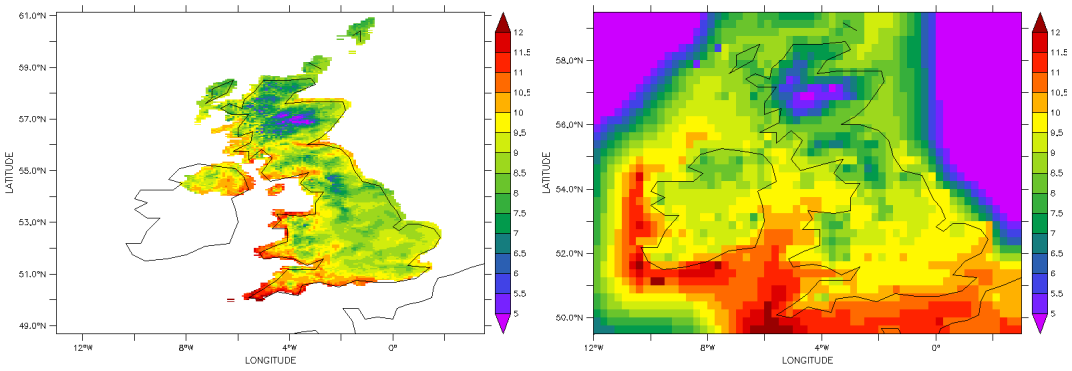

Figure A3.1: Projection vs. observation. The observed annual temperature for the period of 2014 to 2016 (left, UKCP09, land only) was very similar to the predicted annual temperatures for the same period (right, NorESM1-M, RCP4.5, land and sea).

A3.3 Additional Diffusion Simulations

Figure A3.2 and A3.3 visualise *Ae. albopictus*' spread with an RMSD that is either too small or too large.

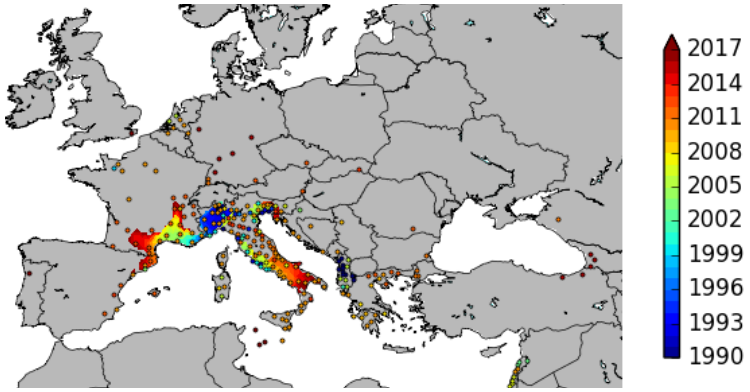

Figure A3.2: Slow mosquito spread Spread of *Ae. albopictus* with an RMSD of 50 m. The mosquito does not get far beyond Italy and the French Riviera in 28 years.

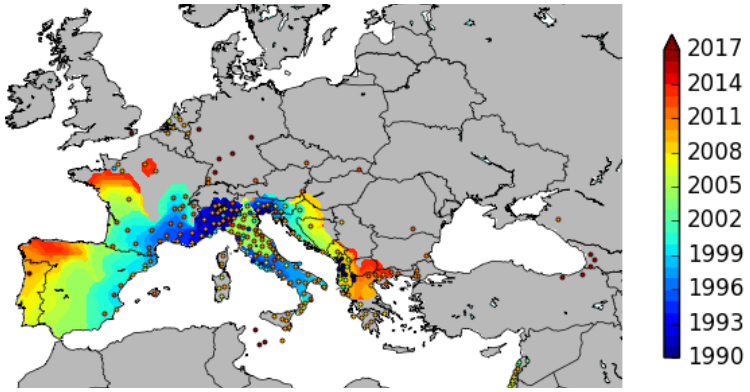

Figure A3.3: Fast mosquito spread Spread of *Ae. albopictus* with an RMSD of 5000 m. Here, the mosquito has spread to large parts of France and Spain by the year 2000.

Using the same RMSD of 1 500 m and setting the detectable threshold to 10^{-40} individuals per hectare shows that mosquitoes get transported over longer distances in very small numbers very quickly, see Figure A3.4. This (unrealistically low detectable threshold) is just to show how a lower threshold leads to a perceived faster spread. Simulated mosquito numbers could also be interpreted as probability of mosquito occurrence, the higher the more likely, with a high chance of mosquito encounters in areas exceeding the threshold of one egg per hectare. We could also integrate these probabilities for certain areas, to give (relative) probabilities of mosquito encounters.

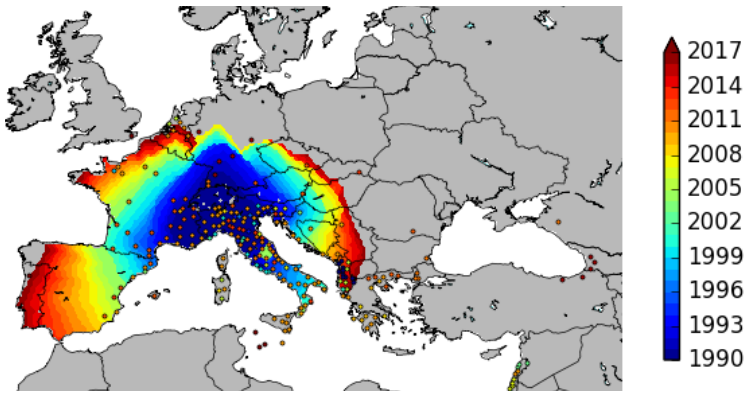

Figure A3.4: Mosquito spread with high detection rate Spread of *Ae. albopictus* with an RMSD of 300 m/day but with a detectable threshold of 10^{-40} individuals per hectare. $M = 0.193$

A3.4 Non-Constant Diffusion Processes

Roche et al. (2015) suggested the speed of *Ae. albopictus*' spread in Europe is increasing over time. We thus analysed the effect of a non-constant diffusion coefficient $D(t)$ with D monotonously increasing with time. The PDE for mature females becomes

$$\partial_t A(x,t) = D(t)\Delta A(x,t) + \delta_\mathrm{I}\, I(x,t) - \mu_\mathrm{A}\, A(x,t).$$

Figure A3.5 shows that the an increase in diffusion spread over time does not improve the

model output. The spread with increasing RMSD looks very similar to the spread with constant RMSD by 2005 (compare Figure 3.4). After 2005, the the mosquito spreads more widely, covering larger areas of Spain, France and Croatia. It is possible that the observed increase in spreading distance per year suggested by Roche et al. (2015) is only visible at smaller scales or in certain years - they only look at *Ae. albopictus* spread in France from 2006 to 2010.

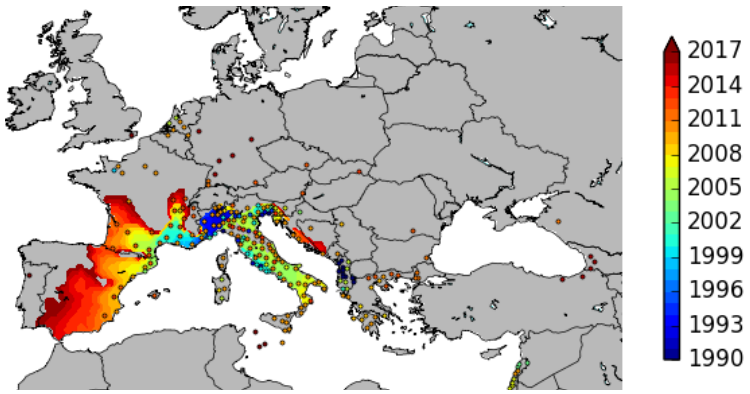

Figure A3.5: Spread of *Ae. albopictus* with a diffusion rate that increases slowly over time. RMSD $= (200 + 10\,Y)$ m with Y being the number of years since 1990. $M = 0.323$.

Finally, we assumed that the mosquito's spread could depend on its location, e.g. mosquitoes could get moved around more often in highly populated areas compared to rural areas. We thus introduced a location-dependent diffusion coefficient $D(x)$ that is proportional to the human population density H:

$$\partial_t A(x,t) = \nabla \cdot (D(x) \nabla A(x,t)) + \delta_\mathrm{I}\, I(x,t) - \mu_\mathrm{A}\, A(x,t)$$

with the nabla operator indicating the divergence ($\nabla\cdot$) and gradient (∇). Again, the resulting output did not increase the model fit to the observed spread, see Figure A3.6.

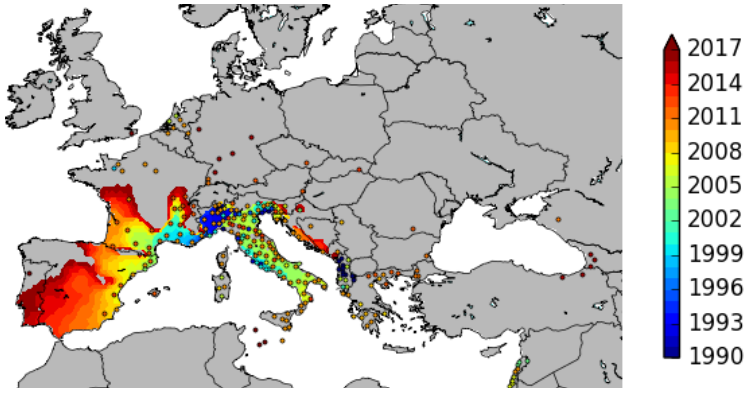

Figure A3.6: Spread of *Ae. albopictus* with a diffusion rate that is higher in densely populated areas. RMSD $= (200 + X)$ m with X being a scaled human population density. $M = 0.329$.

A4.1 Deriving DDEs from ODEs

The terms contributing to the rate of change for each class can be classified into three categories: recruitment, maturation, and mortality. The transformation is demonstrated with the help of class E, eggs.

We assume there are E_0 eggs at $t = t_0$ and, for simplicity, that no eggs are laid after $t = t_0$. Eggs experience a temperature-dependent mortality of $\mu(T(t)) = \mu(t)$:

$$\begin{aligned} E(t_0) &= E_0 \\ \tfrac{d}{dt}E(t) &= -\mu(t)\, E(t). \end{aligned}$$

This equation can easily be integrated to

$$E(t) = E_0\, e^{-\int_{t_0}^{t} \mu(\xi)\, d\xi}$$

and defining $t^\star = t - t_0$ gives

$$E(t) = E(t - t^\star)\, e^{-\int_{t-t^\star}^{t} \mu(\xi)\, d\xi}.$$

After an egg development period of τ_E, all eggs mature to the juvenile stage, thus at $t = \tau_E$:

$$\begin{aligned} \tfrac{d}{dt}E(t)|_{t=\tau_E} &= -\delta_{\tau_E} E(t) \\ &= -\delta_{\tau_E} E(t - \tau_E)\, e^{-\int_{t-\tau_E}^{t} \mu(\xi)\, d\xi} \\ &= -M_E(t), \end{aligned}$$

with $\delta_{\tau_E} = 1/\Delta t$ at τ_E and 0 otherwise. Thus, the whole term, here $E(t)$, will change from class E to the next within this particular time step when $t = \tau_E$. Finally, we include egg recruitment. Class E is recruiting from mature females A with a rate of $\beta\,(1 - \omega)$ (egg laying rate times a factor for diapausing eggs).

$$\begin{aligned} \tfrac{d}{dt}E(t) &= \beta\,(1 - \omega)\, A(t) \\ &= R_E(t) \end{aligned}$$

and

$$E(t_0) = \beta\,(1 - \omega)\, A(t_0).$$

Combining recruitment, maturation, and mortality gives

$$\begin{aligned} \tfrac{d}{dt}E(t) &= R_E(t) - M_E(t) - \mu(t)\, E(t) \\ &= \beta\,(1 - \omega)\, A(t) - E(t - \tau_E)\, e^{-\int_{t-\tau_E}^{t} \mu(\xi)\, d\xi} - \mu(t)\, E(t) \\ &= \beta\,(1 - \omega)\, A(t) - \beta\,(1 - \omega)\, A(t - \tau_E)\, e^{-\int_{t-\tau_E}^{t} \mu(\xi)\, d\xi} - \mu(t)\, E(t). \end{aligned}$$

The same applies to immature female development with a development period of τ_I, and transition of exposed to infectious mosquitoes after the EIP.

Due to larval density dependence and the additional mortality term, juvenile mortality does not follow an exponential decay. Integration of

$$\tfrac{d}{dt}J(t) = -\mu(t)\,J(t) - \frac{J(t)^2}{K(t)}$$

is achieved by substitution of $x(t) := J(t)\,\exp(\int_0^t \mu(\xi)\,d\xi)$. Then

$$x_0 = x(0) = J(0) = J_0$$

and

$$\begin{aligned}
\tfrac{d}{dt}x(t) &= \tfrac{d}{dt}\left(J(t)\,\exp\left(\int_0^t \mu(\xi)\,d\xi\right)\right) \\
&= \left(\tfrac{d}{dt}J(t) + \mu(t)\,J(t)\right)\exp\left(\int_0^t \mu(\xi)\,d\xi\right) \\
&= \left(-\mu(t)\,J(t) - \frac{J(t)^2}{K(t)} + \mu(t)\,J(t)\right)\exp\left(\int_0^t \mu(\xi)\,d\xi\right) \\
&= -\frac{J(t)^2}{K(t)}\exp\left(\int_0^t \mu(\xi)\,d\xi\right) \\
&= -x(t)^2\frac{1}{K(t)}\exp\left(-\int_0^t \mu(\xi)\,d\xi\right).
\end{aligned}$$

Integration yields

$$x(t) = \frac{1}{\int_0^t \frac{1}{K(\xi)}\exp(-\int_0^\xi \mu(\xi)\,d\xi)d\xi + c}$$

with

$$x_0 = x(0) = \frac{1}{c},$$

so that

$$x(t) = \frac{1}{\int_0^t \frac{1}{K(\xi)}\exp(-\int_0^\xi \mu(\xi)d\xi)d\xi + \frac{1}{x_0}}$$

and using back-substitution of $J(t) = x(t)\,\exp(-\int_0^t \mu(\xi)\,d\xi)$ gives

$$\begin{aligned} J(t) &= \frac{\exp(-\int_0^t \mu(\xi)d\xi)}{\int_0^t \frac{1}{K(\xi)} \exp(-\int_0^\xi \mu(\xi)d\xi)d\xi + \frac{1}{J_0}} \\ &= \frac{J_0 \exp(-\int_0^t \mu(\xi)d\xi)}{J_0 \int_0^t L(\xi)d\xi + 1} \end{aligned}$$

with $L(\xi) = \frac{1}{K(\xi)} \exp(-\int_0^\xi \mu(\xi)d\xi)$.

A4.2 Time Delay Calculation

Before we run any simulations, we first calculate development times for immature life stages $(\tau_{E_t}, \tau_{J_t}, \tau_{I_t})$ and the extrinsic incubation period (EIP_t) for the temperatures given at all days of the year $t = 0 \ldots 365$. Starting from any given time point t_0, we sum over all the following inverse development times $\frac{1}{\tau_{X_t}}$, that denote the fraction of daily development, until this sum reaches 1:

$$\tau_X(t) = \inf\{n \in \mathbb{N}^+ : \sum_{t=t_0}^{n} \frac{1}{\tau_{X_t}} \geq 1\}.$$

For example, if for days $t = 1, 2, 3$ temperatures would drop slightly and the juvenile development times would be $\tau_J = 10, 12, 13$ days. We would calculate that after these three days, $\frac{1}{10} + \frac{1}{12} + \frac{1}{13} = 26\%$ of the development would be completed. We would continue to add inverse development times until we reach 100% development and take the final number of days as development period.

A4.3 DDE vs. ODE infection dynamics

The extrinsic incubation period (EIP) is the period a mosquito spends infected but not yet infectious. During this time, the pathogen (the dengue virus in our case) has to replicate and spread in the mosquito before its saliva gets infectious and the pathogen can be transmitted to a person during a bite. There are different ways to model the transition from infected to infectious mosquitoes, e.g. with ordinary differential equations (ODEs) or delayed differential equations (DDEs). Using ODEs or DDEs imposes different assumptions on the infection dynamics.

For this comparison, we will assume that we only have the host and no vector, i.e. infected hosts can infect susceptible hosts like in an influenza outbreak. The same principles are applicable to vector-host models though.

ODE SEI model

SEI denoting susceptible, exposed, and infectious mosquitoes for the infection dynamics. In ODEs, the rate of change of the classes $\mathbf{u} = (S, E, I)$ depends on a reaction function f that describes a linear or non-linear relationship of these classes; $\frac{d}{dt}\mathbf{u}(t) = f(\mathbf{u}(t))$.

The (simplified) equations are given by:

$$\begin{aligned}
\frac{d}{dt}S(t) &= -\beta S(t)I(t) - \mu S(t) \\
\frac{d}{dt}E(t) &= \beta S(t)I(t) - \gamma E(t) - \mu E(t) \\
\frac{d}{dt}I(t) &= \gamma E(t) - \mu E(t)
\end{aligned}$$

with β the infection probability, μ the mortality, and γ the incubation rate, i.e. the inverse of the EIP, $\gamma = \frac{1}{\text{EIP}}$.

DDE SI model

Another approach to model this incubation period are delayed differential equations (DDEs). Here, the rate of change at a certain time not only depends on the current state but also on previous states; $\frac{d}{dt}\mathbf{u}(t) = f(\mathbf{u}(t), \mathbf{u}(t-\tau))$.

A DDE model that corresponds to the ODE SEI model only includes the classes S and I. Here, mosquitoes get infected but stay in the susceptible class until they change to class I when the EIP is over.

$$\begin{aligned}
\frac{d}{dt}S(t) &= -\beta S(t)I(t) - \mu S(t) \\
\frac{d}{dt}E(t) &= \beta S(t)I(t) - \beta S(t-\tau)I(t-\tau)\mathrm{e}^{-\int_{t-\tau}^{t}\mu d\xi} - \mu E(t) \\
\frac{d}{dt}I(t) &= \beta S(t-\tau)I(t-\tau)\mathrm{e}^{-\int_{t-\tau}^{t}\mu d\xi} - \mu I(t)
\end{aligned}$$

The time delay τ is in this case the EIP. The transition of mosquitoes into class I does not start before the EIP is over. But each time step, a certain proportion of mosquitoes die. After the EIP has passed, all the mosquitoes that have not died in the meantime move to class I. The factor $\mathrm{e}^{-\int_{t-\tau}^{t}\mu d\xi}$ denotes for this mortality experienced over the EIP. Note that the incidence rate βSI is written without the delay terms in the susceptible's equation. This is necessary as otherwise infected but not yet infectious individuals remained in the susceptible class for the period τ and could then get infected again. The total number of individuals are then given by $N := S+I+E$.

The DDE model could actually be only calculated with classes S and I, but in our model, we also need to explicitly calculate class E as exposed females also lay eggs.

Comparison

The difference between the two model assumptions becomes clear when comparing single infection cases directly, see Figure A4.1. After a single infection case is introduced from outside at day 0, e.g. through a mosquito bite, the first infectious individual in the ODE model appears at day 1 while it appears only after EIP = 10 days with the DDE model.

Using ODEs assumes that after the end of the EIP, 50% of exposed mosquitoes have become infectious and changed into class I. However: before and after the end of the EIP, there are constantly mosquitoes changing from class E to class I. The distribution of transitions is not

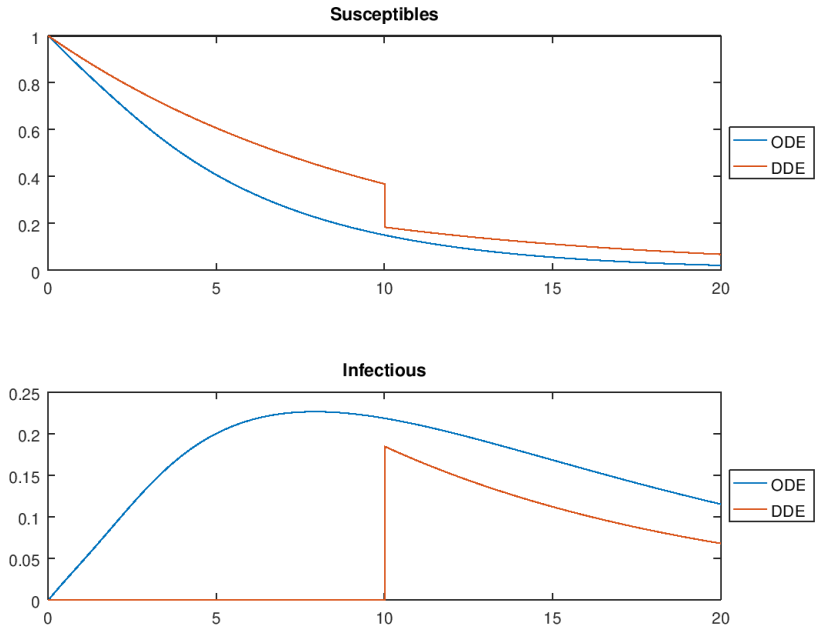

Figure A4.1: Early disease onset. A susceptible meets an infected individual at time $t = 0$. In the DDE model, the number of infectious increases instantly, while it only increases after the EIP in the DDE model.

bell shaped (the transitions are not normally distributed) but rather resembles an exponential decay which is problematic: Most mosquitoes change from class E to I after day 1, regardless of the EIP, and a tiny fraction will still wait to become infectious in 100 years. In contrast, using DDEs assumes that after the end of the EIP, the mosquitoes that do not die in the exposed state, become infectious all at once.

If τ is small, the models give similar results which is in accordance with Kaddar et al. (2011). The more the EIP or τ increases, the more the output of the ODE and DDE models will differ. Figure A4.2 shows the disease dynamics without mortalities for $\tau = 4$ and $\tau = 18$.

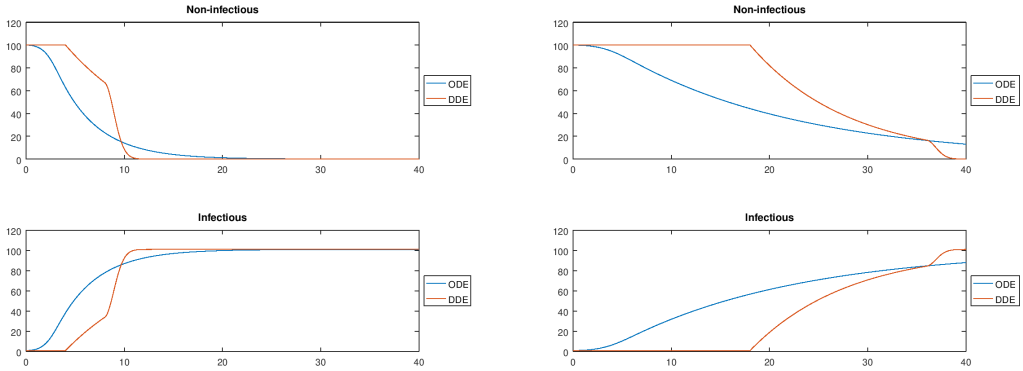

Figure A4.2: Effect of EIP on models. Left: EIP = 4. Both ODE and DDE model show high infected numbers after about 10 days. Right: EIP=18. While the DDE model does not show any infections in the first 18 time steps, the ODE model constantly increases. Both models show similar numbers only after 30 days.

It is thus important to use DDE when analysing disease dynamics in which the EIP can take more than a week due to its temperature-dependence. Otherwise, the length and amplitude of disease outbreaks could be overestimated.

A4.4 DDE Equilibria & Stability

In order to determine model equilibria, we first write down our full equation system:

$$
\begin{aligned}
\tfrac{d}{dt}E(t) &= \beta\,(1-\omega)\,A(t) - \left(\beta\,(1-\omega)\,A(t-\tau_E)\right)\,e^{-\int_{t-\tau_E}^{t}\mu_E(\xi)\,d\xi} - \mu_E\,E(t)\\
\tfrac{d}{dt}J(t) &= \beta\,(1-\omega)\,A(t-\tau_E)\,e^{-\int_{t-\tau_E}^{t}\mu_E(\xi)\,d\xi} + \sigma\,\gamma\,E_d(t)\\
&\quad - \frac{\left(\beta\,(1-\omega)\,A(t-\tau_E-\tau_J)\,e^{-\int_{t-\tau_E-\tau_J}^{t-\tau_J}\mu_E(\xi)\,d\xi} + \sigma\,\gamma\,E_d(t-\tau_J)\right)\,e^{-\int_{t-\tau_J}^{t}\mu_J(\xi)\,d\xi)}}{1+\left(\beta\,(1-\omega)\,A(t-\tau_E-\tau_J)\,e^{-\int_{t-\tau_E-\tau_J}^{t-\tau_J}\mu_E(\xi)\,d\xi} + \sigma\,\gamma\,E_d(t-\tau_J)\right)\int_{t-\tau_J}^{t}L(u)\,du} - \mu_J\,J(t) - \frac{J(t)^2}{K(t)}\\
\tfrac{d}{dt}I(t) &= 0.5\,\frac{\left(\beta\,(1-\omega)\,A(t-\tau_E-\tau_J)\,e^{-\int_{t-\tau_E-\tau_J}^{t-\tau_J}\mu_E(\xi)\,d\xi} + \sigma\,\gamma\,E_d(t-\tau_J)\right)\,e^{-\int_{t-\tau_J}^{t}\mu_J(\xi)\,d\xi)}}{1+\left(\beta\,(1-\omega)\,A(t-\tau_E-\tau_J)\,e^{-\int_{t-\tau_E-\tau_J}^{t-\tau_J}\mu_E(\xi)\,d\xi} + \sigma\,\gamma\,E_d(t-\tau_J)\right)\int_{t-\tau_J}^{t}L(u)\,du}\\
&\quad - 0.5\left(\frac{\left(\beta\,(1-\omega)\,A(t-\tau_E-\tau_J-\tau_I)\,e^{-\int_{t-\tau_E-\tau_J-\tau_I}^{t-\tau_J-\tau_I}\mu_E(\xi)\,d\xi} + \sigma\,\gamma\,E_d(t-\tau_J-\tau_I)\right)\,e^{-\int_{t-\tau_J-\tau_I}^{t-\tau_I}\mu_J(\xi)\,d\xi}}{1+\left(\beta\,(1-\omega)\,A(t-\tau_E-\tau_J-\tau_I)\,e^{-\int_{t-\tau_E-\tau_J-\tau_I}^{t-\tau_J-\tau_I}\mu_E(\xi)\,d\xi} + \sigma\,\gamma\,E_d(t-\tau_J-\tau_I)\right)\int_{t-\tau_J-\tau_I}^{t-\tau_I}L(u)\,du}\right)\\
&\quad \cdot e^{-\int_{t-\tau_I}^{t}\mu_A(\xi)\,d\xi} - \mu_A\,I(t)\\
\tfrac{d}{dt}A(t) &= 0.5\left(\frac{\left(\beta\,(1-\omega)\,A(t-\tau_E-\tau_J-\tau_I)\,e^{-\int_{t-\tau_E-\tau_J-\tau_I}^{t-\tau_J-\tau_I}\mu_E(\xi)\,d\xi} + \sigma\,\gamma\,E_d(t-\tau_J-\tau_I)\right)\,e^{-\int_{t-\tau_J-\tau_I}^{t-\tau_I}\mu_J(\xi)\,d\xi}}{1+\left(\beta\,(1-\omega)\,A(t-\tau_E-\tau_J-\tau_I)\,e^{-\int_{t-\tau_E-\tau_J-\tau_I}^{t-\tau_J-\tau_I}\mu_E(\xi)\,d\xi} + \sigma\,\gamma\,E_d(t-\tau_J-\tau_I)\right)\int_{t-\tau_J-\tau_I}^{t-\tau_I}L(u)\,du}\right)\\
&\quad \cdot e^{-\int_{t-\tau_I}^{t}\mu_A(\xi)\,d\xi} - \mu_A\,A(t)\\
\tfrac{d}{dt}E_d(t) &= \beta\,\omega\,A(t) - \sigma\,E_d(t)
\end{aligned}
$$

We now assume that temperature and precipitation are constant and thus that all parameters are stable too: $\mu_E(T(t)) = \mu_E,\ \tau_E(T(t)) = \tau_E$, etc. We get:

$$
\begin{aligned}
\tfrac{d}{dt}E(t) &= \beta\,(1-\omega)\,A(t) - \left(\beta\,(1-\omega)\,A(t-\tau_E)\right)\,e^{-\tau_E\,\mu_E} - \mu_E E(t)\\
\tfrac{d}{dt}J(t) &= \beta\,(1-\omega)\,A(t-\tau_E)\,e^{-\tau_E\,\mu_E} + \sigma\,\gamma\,E_d(t)\\
&\quad - \frac{\left(\beta\,(1-\omega)\,A(t-\tau_E-\tau_J)\,e^{-\tau_E\,\mu_E} + \sigma\,\gamma\,E_d(t-\tau_J)\right)e^{-\tau_J\mu_J}}{1+\left(\beta\,(1-\omega)\,A(t-\tau_E-\tau_J)\,e^{-\tau_E\,\mu_E} + \sigma\,\gamma\,E_d(t-\tau_J)\right)\frac{\tau_J}{K}e^{-\tau_J\mu_J}} - \mu_J J(t) - \frac{J(t)^2}{K}\\
\tfrac{d}{dt}I(t) &= 0.5\frac{\left(\beta\,(1-\omega)\,A(t-\tau_E-\tau_J)\,e^{-\tau_E\,\mu_E} + \sigma\,\gamma\,E_d(t-\tau_J)\right)e^{-\tau_J\mu_J}}{1+\left(\beta\,(1-\omega)\,A(t-\tau_E-\tau_J)\,e^{-\tau_E\,\mu_E} + \sigma\,\gamma\,E_d(t-\tau_J)\right)\frac{\tau_J}{K}e^{-\tau_J\mu_J}}\\
&\quad - 0.5\frac{\left(\beta\,(1-\omega)\,A(t-\tau_E-\tau_J-\tau_I)\,e^{-\tau_I\,\mu_A} + \sigma\,\gamma\,E_d(t-\tau_J-\tau_I)\right)e^{-\tau_J\mu_J}}{1+\left(\beta\,(1-\omega)\,A(t-\tau_E-\tau_J-\tau_I)\,e^{-\tau_I\,\mu_A} + \sigma\,\gamma\,E_d(t-\tau_J-\tau_I)\right)\frac{\tau_J}{K}e^{-\tau_J\mu_J}}e^{-\tau_I\,\mu_A} - \mu_A I(t)\\
\tfrac{d}{dt}A(t) &= 0.5\frac{\left(\beta\,(1-\omega)\,A(t-\tau_E-\tau_J-\tau_I)\,e^{-\tau_I\,\mu_A} + \sigma\,\gamma\,E_d(t-\tau_J-\tau_I)\right)e^{-\tau_J\mu_J}}{1+\left(\beta\,(1-\omega)\,A(t-\tau_E-\tau_J-\tau_I)\,e^{-\tau_I\,\mu_A} + \sigma\,\gamma\,E_d(t-\tau_J-\tau_I)\right)\frac{\tau_J}{K}e^{-\tau_J\mu_J}}e^{-\tau_I\,\mu_A} - \mu_A A(t)\\
\tfrac{d}{dt}E_d(t) &= \beta\,\omega A(t) - \sigma E_d(t).
\end{aligned}
$$

At equilibria DDEs behave like ODEs, as in the limit $x(t-\tau) = x(t)$. Thus we get:

$$\frac{d}{dt}E = \beta\,(1-\omega)\,A\,(1-e^{-\tau_E\,\mu_E}) - \mu_E\,E$$

$$\frac{d}{dt}J = \left(\beta\,(1-\omega)\,A\,e^{-\tau_E\,\mu_E} + \sigma\,\gamma\,E_d\right)\left(1 - \frac{e^{-\tau_J\,\mu_J}}{1+\left(\beta\,(1-\omega)\,A\,e^{-\tau_E\,\mu_E} + \sigma\,\gamma\,E_d\right)\frac{\tau_J}{K}e^{-\tau_J\,\mu_J}}\right) - \mu_J\,J - \frac{J^2}{K}$$

$$\frac{d}{dt}I = 0.5\frac{\left(\beta\,(1-\omega)\,A\,e^{-\tau_E\,\mu_E} + \sigma\,\gamma\,E_d\right)e^{-\tau_J\,\mu_J}}{1+\left(\beta\,(1-\omega)\,A\,e^{-\tau_E\,\mu_E} + \sigma\,\gamma\,E_d\right)\frac{\tau_J}{K}e^{-\tau_J\,\mu_J}}(1-e^{-\tau_I\,\mu_A}) - \mu_A\,I$$

$$\frac{d}{dt}A = 0.5\frac{\left(\beta\,(1-\omega)\,A\,e^{-\tau_I\,\mu_A} + \sigma\,\gamma\,E_d\right)e^{-\tau_J\,\mu_J}}{1+\left(\beta\,(1-\omega)\,A\,e^{-\tau_I\,\mu_A} + \sigma\,\gamma\,E_d\right)\frac{\tau_J}{K}e^{-\tau_J\,\mu_J}}e^{-\tau_I\,\mu_A} - \mu_A\,A$$

$$\frac{d}{dt}E_d = \beta\,\omega\,A - \sigma\,E_d$$

Assuming E, J, I, A, E_d all positive, we get a trivial, $x_1^\star = 0$, and a non-trivial solution, $x_2^\star = (E^\star, J^\star, I^\star, A^\star, E_d^\star)$, with

$$A^\star = \frac{1}{2}\frac{K(\gamma\beta\omega e^{-\mu_J\tau_J-\mu_A\tau_I} + \beta(1-\omega)\,e^{-\mu_E\tau_E-\mu_J\tau_J-\mu_A\tau_I} - 2\mu_A)}{(\gamma\beta\omega + \beta(1-\omega)e^{-\mu_E\tau_E})\mu_A\tau_J e^{-\mu_J\tau_J}}$$

$$E_d^\star = \frac{\beta\omega}{\sigma}A^\star$$

$$E^\star = \frac{\beta(1-\omega)(1-e^{-\mu_E\tau_E})}{\mu_E}A^\star$$

and $I^\star$ and $J^\star$ being longer terms we do not write down.
It is now of interested for what parameter range either equilibrium is stable. If the trivial equilibrium is stable, the mosquito population will not be able to successfully reproduce in the long run.

Stability

We now analyse the stability of the trivial equilibrium. Let $x^\star$ be an equilibrium of equation

$$\frac{d}{dt}x(t) = f(x, x(t-\tau_1), \ldots x(t-\tau_n)), \tag{6.1}$$

and let $\delta x(t)$ be the displacement from this equilibrium, assumed small, at any time in the open interval $[t_0, \infty)$. Accordingly,

$$x(t) = x^\star + \delta x(t)$$

and

$$\frac{d}{dt}x(t) = \frac{d}{dt}\delta x(t) = f(x^\star + \delta x(t), x^\star + \delta x(t-\tau_1), \ldots x^\star + \delta x(t-\tau_n)).$$

Linearisation, using a Taylor series, yields

$$\frac{d}{dt}\delta x(t) \approx J_0\delta x(t) + J_{\tau_1}\delta x(t-\tau_1) + \ldots J_{\tau_n}\delta x(t-\tau_n)$$

with J_0 being the Jacobian with respect to x, and J_{τ_i} being the Jacobians with respect to $x(t-\tau_i)$, evaluated at $x(t) = x(t-\tau_1) = \ldots x(t-\tau_n) = x^\star$. Following Roussel (2005), we now assume that equation 6.1 has an exponential solution, so that we can write $\delta x(t) = Be^{\lambda t}$, and

thus we get

$$\begin{aligned}\frac{d}{dt}\delta x(t) &= J_0 B e^{\lambda t} + J_{\tau_1} B e^{\lambda(t-\tau_1)} + \dots J_{\tau_n} B e^{\lambda(t-\tau_n)} \\ &= (J_0 + J_{\tau_1} e^{-\lambda\tau_1} + \dots J_{\tau_n} e^{-\lambda\tau_n}) B e^{\lambda t}\end{aligned}$$

and finally our characteristic equation with I being the identity matrix

$$|J_0 + J_{\tau_1} e^{-\lambda\tau_1} + \dots J_{\tau_n} e^{-\lambda\tau_n} - \lambda I| = 0.$$

Calculating the Jacobian matrices at the zero equilibrium $x^\star = 0$ gives

$$J_0 = \begin{pmatrix} -\mu_E & & & \beta(1-\omega) & \\ & -\mu_J & & & \sigma\gamma \\ & & -\mu_A & & \\ & & & -\mu_A & \\ & & & \beta\omega & -\sigma \end{pmatrix}$$

as the normal Jacobian with respect to $x(t)$ and Jacobians J_{τ_E}, J_{τ_J}, $J_{\tau_E+\tau_J}$,... with respect to $x(t-\tau_E)$, $x(t-\tau_J)$, $x(t-\tau_E-\tau_J)$,..., respectively.

As all our DDEs only have delays for A and E_d, the remaining Jacobians J_{τ_E}, J_{τ_J}, $J_{\tau_E+\tau_J}$,... only have entries in the last two columns. Thus, the upper left 3×3 submatrix of the Jacobian combination will stay a diagonal matrix. We see that only entries in the bottom right 2×2 submatrix will affect the determinant of the Jacobians combination. These entries are $\frac{\partial A}{\partial A(t-\tau_E-\tau_J-\tau_I)}$ and $\frac{\partial A}{\partial E_d(t-\tau_J-\tau_I)}$, and assuming constant parameters, $\mu_E(T(t)) = \mu_E, \dots$ gives:

$$\begin{aligned}\frac{\partial A}{\partial A(t-\tau_E-\tau_J-\tau_I)}|_{x=0} &= 0.5\,\beta\,(1-\omega)\,e^{-\int_{t-\tau_E-\tau_J-\tau_I}^{t-\tau_J-\tau_I}\mu_E(\xi)d\xi} e^{-\int_{t-\tau_J-\tau_I}^{t-\tau_I}\mu_J(\xi)d\xi} e^{-\int_{t-\tau_I}^{t}\mu_A(\xi)d\xi} \\ &= 0.5\,\beta\,(1-\omega) e^{-\tau_E\,\mu_E-\tau_J\mu_J-\tau_I\,\mu_A} \\ \frac{\partial A}{\partial E_d(t-\tau_J-\tau_I)}|_{x=0} &= 0.5\,\sigma\,\gamma\,e^{-\int_{t-\tau_J-\tau_I}^{t-\tau_I}\mu_J(\xi)d\xi} e^{-\int_{t-\tau_I}^{t}\mu_A(\xi)d\xi} \\ &= 0.5\,\sigma\,\gamma\,e^{-\tau_J\mu_J-\tau_I\,\mu_A}.\end{aligned}$$

For our characteristic equation, we get

$$|J_0 + e^{-\lambda(\tau_E+\tau_J+\tau_I)} J_{\tau_E+\tau_J+\tau_I} + e^{-\lambda(\tau_J+\tau_I)} J_{\tau_J+\tau_I} - \lambda I| = 0,$$

and calculating the determinant yields:

$$\begin{aligned}(-\mu_E-\lambda)(-\mu_J-\lambda)(-\mu_A-\lambda)\Big[\Big(&-\mu_A + 0.5\,\beta\,(1-\omega)\,e^{-\tau_E\,\mu_E-\tau_J\,\mu_J-\tau_I\,\mu_A}\,e^{-\lambda(\tau_E+\tau_J+\tau_I)} \\ &-\lambda\Big)(-\sigma-\lambda) - \beta\,\omega\,0.5\,\sigma\,\gamma\,e^{\tau_J\mu_J+\tau_I\,\mu_A}\,e^{-\lambda(\tau_J+\tau_I)}\Big] = 0.\end{aligned}$$

Thus

$$\begin{aligned}
&\lambda = -\mu_E \quad \vee \quad \lambda = -\mu_J \quad \vee \quad \lambda = -\mu_A \quad \vee \\
&0 = \left(-\mu_A + 0.5\,\beta\,(1-\omega)\,e^{-\tau_E\,\mu_E - \tau_J\,\mu_J - \tau_I\,\mu_A}\,e^{-\lambda(\tau_E+\tau_J+\tau_I)} - \lambda\right)(-\sigma-\lambda) \\
&\qquad\qquad - \beta\,\omega\,0.5\,\sigma\,\gamma\,e^{-\tau_J\,\mu_J - \tau_I\,\mu_A}\,e^{-\lambda(\tau_J+\tau_I)}
\end{aligned}$$

Substitution of $\lambda := u + iv$ and using Euler's formula gives two equations that show that λ can be real or complex, with either positive or negative real parts. We thus try to reduce the complexity and only look at the active mosquito season with $\omega = 0$ and $\sigma = 0$ to calculate λ for our standard parameter set. We get:

$$0 = \left(-\mu_A + 0.5\,\beta\,e^{-\tau_E\,\mu_E - \tau_J\,\mu_J - \tau_I\,\mu_A}\,e^{-\lambda\,(\tau_E+\tau_J+\tau_I)} - \lambda\right)(-\sigma-\lambda)$$

and thus

$$\begin{aligned}
&\lambda = -\sigma \\
&\quad \vee \\
&\lambda = 0.5\,\beta\,e^{-\tau_E\,(\mu_E-\mu_A) - \tau_J\,(\mu_J-\mu_A) - W(0.5\,\beta\,\tau_E+\tau_J+\tau_I)\,e^{-\tau_E\,(\mu_E-\mu_A) - \tau_J\,(\mu_J-\mu_A)})} - \mu_A,
\end{aligned}$$

with $W(x)$ denoting the Lambert-W function. Calculating λ with actual values for $\tau_E(T)$, $\mu_A(T)$ etc., shows if the trivial equilibrium is stable or unstable. In this case, the population reaches a non-trivial equilibrium for the current model setting when the constant temperature is higher than 16.5 °C and lower than 32.5 °C. Thus, the temperature of the active mosquito season (roughly April until end of September) should be between these two values for a successful establishment of *Ae. albopictus*.

Note that the suitable temperature range obtained with the DDE model is more constrained than the one obtained with the ODE model (13 to 32 °C), compare appendix A2.6.

A5.1 Two Vector R_0 Model

Turner et al. (2013) derive the following formula for a two-host two-vector R_0 model:

$$R_0 = \sqrt{0.5\left(R_{11} + R_{22} + \sqrt{(R_{11} + R_{22})^2 - 4\left(R_{11}\,R_{22} - R_{12}\,R_{21}\right)}\right)}$$

with

$$\begin{aligned}
R_{11} &= \left(\frac{b_1\,\beta_1\,a_1^2}{\mu_1}\right)\left(\frac{\nu_1}{\nu_1+\mu_1}\right)\left(\frac{\Phi_1^2\,m_{A1}}{r_A+d_A} + \frac{(1-\Phi_1)^2\,m_{B1}}{r_B+d_B}\right)\\
R_{22} &= \left(\frac{b_2\,\beta_2\,a_2^2}{\mu_2}\right)\left(\frac{\nu_2}{\nu_2+\mu_2}\right)\left(\frac{\Phi_2^2\,m_{A2}}{r_A+d_A} + \frac{(1-\Phi_2)^2\,m_{B2}}{r_B+d_B}\right)\\
R_{12} &= \left(\frac{b_2\,\beta_1\,a_2\,a_1}{\mu_2}\right)\left(\frac{\nu_2}{\nu_2+\mu_2}\right)\left(\frac{\Phi_2\,\Phi_1\,m_{A1}}{r_A+d_A} + \frac{(1-\Phi_2)(1-\Phi_1)\,m_{B1}}{r_B+d_B}\right)\\
R_{21} &= \left(\frac{b_1\,\beta_2\,a_1\,a_2}{\mu_1}\right)\left(\frac{\nu_1}{\nu_1+\mu_1}\right)\left(\frac{\Phi_1\,\Phi_2\,m_{A2}}{r_A+d_A} + \frac{(1-\Phi_1)(1-\Phi_2)\,m_{B2}}{r_B+d_B}\right)
\end{aligned}$$

for vector species 1 and 2, and host species A and B. Here, R_{ij} gives the square root of the basic reproduction number for secondary infection of vector i caused by first infections from vector j.

As we neglect any sylvatic cycles in our simulations, i.e. transmission pathways between vectors and wild animals, we only have one host: humans. The terms can thus be reduced to

$$\begin{aligned}
R_{11} &= \left(\frac{b_1\,\beta_1\,a_1^2}{\mu_1}\right)\left(\frac{\nu_1}{\nu_1+\mu_1}\right)\left(\frac{\Phi_1^2\,m_1}{r+d}\right)\\
R_{22} &= \left(\frac{b_2\,\beta_2\,a_2^2}{\mu_2}\right)\left(\frac{\nu_2}{\nu_2+\mu_2}\right)\left(\frac{\Phi_2^2\,m_2}{r+d}\right)\\
R_{21} &= \left(\frac{b_1\,\beta_2\,a_1\,a_2}{\mu_1}\right)\left(\frac{\nu_1}{\nu_1+\mu_1}\right)\left(\frac{\Phi_1\,\Phi_2\,m_2}{r+d}\right)\\
R_{12} &= \left(\frac{b_2\,\beta_1\,a_2\,a_1}{\mu_2}\right)\left(\frac{\nu_2}{\nu_2+\mu_2}\right)\left(\frac{\Phi_2\,\Phi_1\,m_1}{r+d}\right).
\end{aligned}$$

With

$$\begin{aligned}
R_{21}\cdot R_{12} &= \left(\frac{b_1\,\beta_2\,a_1\,a_2}{\mu_1}\right)\left(\frac{\nu_1}{\nu_1+\mu_1}\right)\left(\frac{\Phi_1\,\Phi_2\,m_2}{r+d}\right)\left(\frac{b_2\,\beta_1\,a_2\,a_1}{\mu_2}\right)\left(\frac{\nu_2}{\nu_2+\mu_2}\right)\left(\frac{\Phi_2\,\Phi_1\,m_1}{r+d}\right)\\
&= \left(\frac{b_1\,\beta_1\,a_1^2}{\mu_1}\right)\left(\frac{\nu_1}{\nu_1+\mu_1}\right)\left(\frac{\Phi_1^2\,m_1}{r+d}\right)\left(\frac{b_2\,\beta_2\,a_2^2}{\mu_2}\right)\left(\frac{\nu_2}{\nu_2+\mu_2}\right)\left(\frac{\Phi_2^2\,m_2}{r+d}\right)\\
&= R_{11}\cdot R_{22},
\end{aligned}$$

it follows that

$$\begin{aligned} R_0 &= \sqrt{0.5\left(R_{11} + R_{22} + \sqrt{(R_{11} + R_{22})^2 - 4\left(R_{11}\,R_{22} - R_{12}\,R_{21}\right)}\right)} \\ &= \sqrt{0.5\left(R_{11} + R_{22} + \sqrt{(R_{11} + R_{22})^2}\right)} \\ &= \sqrt{R_{11} + R_{22}}. \end{aligned}$$

This equation was used to analyse the Zika outbreak in Brazil. For Europe, where we effectively only have *Ae. albopictus* as a single vector (there might be other local species competent for disease transmission though (Blagrove *et al.*, unpublished)), this equation[3] is further reduced to

$$\begin{aligned} R_0 &= \sqrt{R_{11}} \\ &= \sqrt{\left(\frac{b_1\,\beta_1\,a_1^2}{\mu_1}\right)\left(\frac{\nu_1}{\nu_1 + \mu_1}\right)\left(\frac{\Phi_1^2\,m_1}{r + d}\right)} \end{aligned}$$

Note that with this approach, we get the average of hosts infected by a single vector, respectively vectors infected by a single host. If $R_0 = 3$, then one infected human could infect three mosquitoes, and one infected mosquito could infect three humans (or one human infects one mosquito and one mosquito infects nine humans). This definition, albeit cumbersome, is often used in vector-borne disease outbreaks, both calculated with mathematical models (Villela et al., 2017) or derived by data (Nishiura et al., 2016). Other studies use the more intuitive definition of like-to-like transmission of $R_0^\star$, i.e. how many infections in humans arise from a single infected human case (Poletti et al., 2011; Manica et al., 2017). Both definitions are closely related and values can be converted by $R_0^\star = R_0^2$, it is just important to be aware of the difference in scale to not compare apples with oranges.

A5.2 R_0 Model Parametrisation

The parametrisation of the R_0 model requires vector-specific parameters such as biting rates, host preference, mosquito mortalities and mosquito-to-human ratios. It also requires virus-specific parameters (that often depend on the vector too), such as virus transmission probabilities from host to vector and vice versa (vector competence for the virus), the extrinsic incubation period (EIP) and the human recovery rate.

[3] Note the similarity to the formula for the vectorial capacity, VC (Garrett-Jones, 1964), often used in modelling studies (e.g. Liu-Helmersson et al., 2014; Brady et al., 2014):

$$\text{VC} = \frac{b_1\,\beta_1\,a_1^2 m_1 e^{-\mu_1\,\nu_1}}{\mu_1}.$$

The VC is defined as the daily rate at which future infections arise from a currently infective case (Dye, 1986).

A5.2.1 Vector parameters

Biting rates

Data for *Ae. aegypti* biting rates came from Scott et al. (2000) and the fitting of a linear function was done by Liu-Helmersson et al. (2014). For *Ae. albopictus*, we divided this biting rate by half, according to Farjana and Tuno (2013), see Figure A5.1 and Table A5.1.

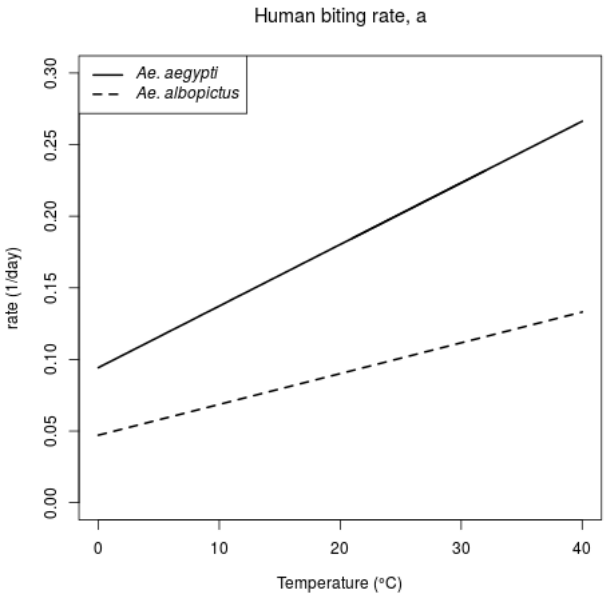

Figure A5.1: Biting rates Both biting rates increase linearly with temperature but *Ae. aegypti* bites more frequent.

Table A5.1: Biting rates for *Aedes* vectors, depending on temperature T.

Parameter	Vector	Biting rate
a_1	*Ae. aegypti*	$0.0043\,T + 0.0943$
a_2	*Ae. albopictus*	$0.5 \cdot (0.0043\,T + 0.0943)$

Host preference

Ae. aegypti is known to preferentially feed on humans and thus has a host preference for humans of 100% (Ponlawat and Harrington, 2005; Kamgang et al., 2012; Sivan et al., 2015). *Ae. albopictus* is more opportunistic in its feeding behaviour, feeding on other mammals, birds and even reptiles and amphibians (Niebylski et al., 1994). Human blood meal ratio was reported to be between 8% and 25% (Savage et al., 1993; Richards et al., 2006), 50% (Faraji et al., 2014; Sivan et al., 2015), 80% (Delatte et al., 2010), or near 100% (Ponlawat and Harrington, 2005; Kamgang et al., 2012). It was thus assumed that *Ae. albopictus* has a human host preference of 50%, see Table A5.2.

Table A5.2: Host preference for *Aedes* vectors.

Parameter	Vector	Human host preference
Φ_1	*Ae. aegypti*	100%
Φ_2	*Ae. albopictus*	50%

Adult mosquito mortality

We use daily mortality rates for adult mosquitoes in the field, derived from a meta-analysis study for both *Aedes* species by Brady et al. (2013), see Figure A5.2 and Table A5.3. Here, a (discontinuous) function, different to the one in section 2.2.1, was fitted to the data, compare Figure A2.2. The difference is minimal and does not affect results.

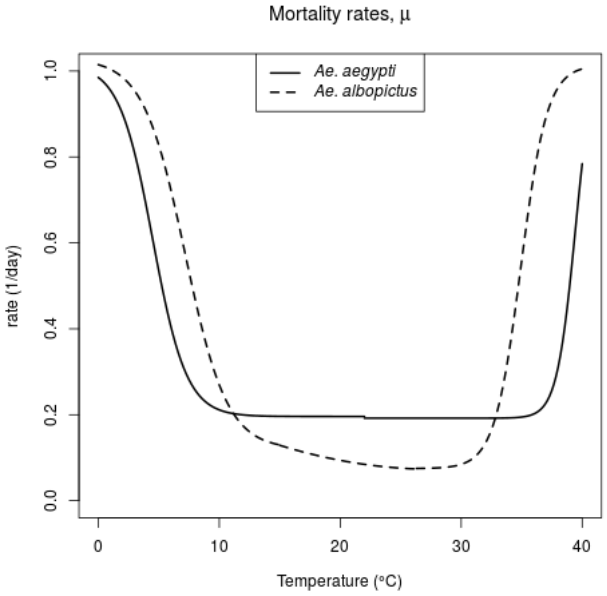

Figure A5.2: Mosquito mortality Shown are daily mortality rates for adult female mosquitoes.

Table A5.3: Mosquito mortality for *Aedes* vectors, depending on temperature T.

Parameter	Vector	Daily mortality rate
μ_1	*Ae. aegypti*	$\begin{cases} (1.22 + \exp(-3.05 + 0.0.72\,T))^{-1} + 0.196 & \text{for } T < 22°C \\ (1.14 + \exp(51.4 - 1.3\,T))^{-1} + 0.192 & \text{for } T \geq 22°C \end{cases}$
μ_2	*Ae. albopictus*	$\begin{cases} (1.1 + \exp(-4.04 + 0.576\,T))^{-1} + 0.12 & \text{for } T < 15°C \\ 0.0003394\,T^2 - 0.01889\,T + 0.336 & \text{for } 15°C \leq T < 26.3°C \\ (1.065 + \exp(32.2 - 0.92\,T))^{-1} + 0.07476 & \text{for } T \geq 26.3°C \end{cases}$

Vector to host ratio

Estimating the vector to host ratio was one of the main difficulties we had to deal with, as there is no systematic data, especially not on a global scale. The global mapping of *Ae. aegypti* and *Ae. albopictus* by Kraemer et al. (2015) gave probabilities of mosquito occurrence which we tried to translate into abundance data. To do this, we first screened the literature for mark-release-recapture (MRR) studies, that give estimates of mosquito numbers or densities, see Table A5.4. If estimates had not been given in the article, the Bayesian estimate was used to calculate densities: $\hat{N} = \frac{(K-1)(n-1)}{k-2} - \delta K$, with K denoting the number of animals marked and released, n the total number of animals captured, and k the number of recaptured animals that were marked. $\delta = 1$ if released mosquitoes come from the laboratory and $\delta = 0$ if they were caught in the area. Dividing by the study area gives an estimated mosquito density $\hat{d}$ in individuals per hectare.
In a next step, we tried to find a reasonable relationship between mosquito numbers and estimated probabilities. Assuming a random distribution of mosquitoes and using the inverse Poisson distribution, the probabilities can be translated into abundances:

$$P(x) = \frac{\lambda^x}{x!} e^{-\lambda}$$

with x being the number of mosquitoes and λ the average number expected. Unfortunately, the resulting values needed further scaling and capping and the probabilities data from Kraemer et al. (2015) do not meet the conditions of the Poisson distribution. In the end, we decided to use a vary simple linear relationship, multiplying the probabilities P with a factor of 1 000 to estimate vector-to-host ratios. This approach is of course independent of human population but gave reasonable results for Latin America, with R_0 values being in the range of what was observed during the Zika outbreak in Brazil (Nishiura et al., 2016; Villela et al., 2017). Moreover, it gave values for mosquito-to-human estimates that were in the range of what was observed for some (sub-)tropical locations with bites per human per day studies (Almeida et al., 2005).

For Europe, we could use a more realistic approach. We had European mosquito estimates derived with our *Ae. albopictus* model from chapter 2. *Ae. aegypti* was excluded from the simulations as this species is not present on the European continent. To estimate mosquito numbers, we used results from chapter 3, in which we apply the developed model and estimate mosquito numbers in Western and Central Europe from the introduction event in 1990, following their spread until 2017. Resulting mosquito numbers V were then set in relation to human numbers H, from the GPWv4 data set (Doxsey-Whitfield et al., 2015), see Table A5.5. Compared to chapters 2 and 3, the vector life cycle model was run with a carrying capacity parameter downscaled by the factor 10 in order to get vector-to-host ratios in the range of 1-35 (Poletti et al., 2011; Manica et al., 2017). Though the original parametrisation gave good estimates for absolute mosquito numbers in certain locations like Rome (Marini et al., 2010) (compare chapter 2), it gave too high ratios when related to human population densities, especially in more rural areas.

Table A5.4: Mosquito abundance Shown are population density estimates for *Ae. albopictus* and *Ae. aegypti* in different regions. Probabilities estimates from Kraemer et al. (2015).

Ae. albopictus

	$\hat{d}$	Date	Prob.	Region	Lat; Long	Reference
♂	1544					
♀	2208	2010, Mar				
♂	520					
♀	604	2010, Jun	87.8%	Réunion	- 21.3208; 55.4844	Gouagna et al. (2015)
♂	76					
♀	-	2010, Sep				
♂	932					
♀	-	2010, Dec				
♂	2566[a]					
♀	-	2007, May	87.8%	Réunion	- 21.3156; 55.4869	Lacroix et al. (2009)
♂	1121[ab]					
♀	203[ab]	2007, Jun				
♂	2337[ac]				41.9028;	
♀	1393[ac]	2008, Sep	57.4%	Italy, Rome	12.5144	Marini et al. (2010) [a]
♂	2019[ad]				21.3167;	
♀	828[ad]	1944, Sep	80.2%	Hawaii	-157.8333	Bonnet and Worcester (1946)

Ae. aegypti

	$\hat{d}$	Date	Prob.	Region	Lat; Long	Reference
♂	55				- 3.9167;	
♀	138	1972, Apr	83.1%	Rabai, Kenya	39.5833	Trpis and Hausermann (1986)
♂	-					
♀	10[ae]	2006, Nov	84.9%	Rio, Brazil		Maciel-de Freitas et al. (2008)
♂	-					
♀	140	2012, Sep	84%	Rio, Brazil	- 22.8750; - 43.2336	Villela et al. (2015)
♂	-					
♀	540	2013, Mar				
♂	-				8.9530;	
♀	83	2010, Mar	76%	Panama	- 79.6975	Neira et al. (2014)

Calculated with Bayesian estimator.

[b] Average of two trials.

[c] Average of three trials.

[d] As female abundance was not given, it was calculated with their male to female sex ratio of 1:0.41.

[e] They do not specify their recapture area, thus the small density.

A5.2.2 Virus parameters

At the time of the big outbreak in Brazil, Zika was not studied in great detail. It was thus necessary to estimate parameters for Zika virus transmission from the closely related dengue virus, compare Figure 1.2.

Table A5.5: Vector-to-host ratios for *Aedes* vectors in the simulations for South America and Europe.

South America

Parameter	Vector	Vector-to-host ratio
m_1	*Ae. aegypti*	1000 P_1
m_2	*Ae. albopictus*	1000 P_2

Europe

Parameter	Vector	Vector-to-host ratio
m_1	*Ae. aegypti*	0
m_2	*Ae. albopictus*	V/H

Transmission probability

Both virus transmission probability from vector to human and from human to vector are complicated to estimate. The transmission process depends on the virus concentration in the human blood or in the mosquito saliva, respectively (Nguyen et al., 2013; Carrington and Simmons, 2014) and some studies even assume a temperature-dependent process (Liu-Helmersson et al., 2014). To estimate the transmission probability from host to vector, laboratory studies often measure the rate of positive mosquitoes after certain days post infection (DPI). They can either examine virus concentration in mosquito legs or thorax, in the mosquito head, or in the saliva (Heitmann et al., 2018) and differences can be crucial for vector competence. For example, the thorax of *Ae. albopictus* is much faster infected with dengue virus type-2 compared to *Ae. aegypti*. But the virus only slowly reaches *Ae. albopictus*' head and saliva, if at all, so that *Ae. aegypti* is much more competent to transmit dengue (Lambrechts et al., 2010). Of course, the transmission probability from vector to human cannot be tested in studies and thus has to be estimated.[4]

Dengue *Ae. aegypti* is more competent in transmitting the dengue virus not only due to its human host preference and higher biting rate but also due to its higher probability of becoming infectious (Lambrechts et al., 2010), see Table A5.6.

Table A5.6: Dengue transmission probability for *Aedes* vectors from human to vector and from vector to human.

Parameter	Vector	Value	Range	References
b_1	*Ae. aegypti*	0.5	0.33-0.75	Newton and Reiter (1992) Manore et al. (2014)
b_2	*Ae. albopictus*	0.5	0.1-0.5	Manore et al. (2014)
β_1	*Ae. aegypti*	0.5	0.15-0.75	Newton and Reiter (1992) Paupy et al. (2010) Manore et al. (2014)
β_2	*Ae. albopictus*	0.31	0.1-0.45	Paupy et al. (2010) Manore et al. (2014)

[4]Some studies use the positivity rate of mosquito thorax infection as transmission probability from human to vector, and the positivity rate of mosquito saliva as probability from vector to human.

Chikungunya Due to mutations in an envelope protein genes E1 and E2, *Ae. albopictus* has acquired a high competence to transmit this virus, relative to *Ae. aegypti* (Tsetsarkin et al., 2007; Tsetsarkin and Weaver, 2011), see Table A5.7. As the recent chikungunya outbreaks in 2007 and 2014 were caused by mutated strains (Ciocchetta et al., 2018), we decided to parametrise out model for this virus strain.

Table A5.7: Chikungunya transmission probability for *Aedes* vectors from human to vector and from vector to human.

Parameter	Vector	Value	Range	References
b_1	*Ae. aegypti*	0.24	0.001-0.35	Manore et al. (2014)
b_2	*Ae. albopictus*	0.7	0.33-0.8	Dumont et al. (2008) Dumont and Chiroleu (2010) Manore et al. (2014)
β_1	*Ae. aegypti*	0.24	0.04-0.95	Pesko et al. (2009) Paupy et al. (2010) Manore et al. (2014)
β_2	*Ae. albopictus*	0.6	0.19-1	Vazeille et al. (2007) Dumont et al. (2008) Pesko et al. (2009) Paupy et al. (2010) Vega-Rúa et al. (2014) Alto et al. (2017) Heitmann et al. (2018)

Zika Zika was not very well studied until the outbreak in 2015 and thus there was nearly no data available. Chouin-Carneiro et al. (2016) measured infection probabilities in the vector but for transmission probabilities to humans, we had to use parameters derived for dengue, see Table A5.8.

Table A5.8: Zika transmission probability for *Aedes* vectors from human to vector and from vector to human.

Parameter	Vector	Value	References
b_1	*Ae. aegypti*	0.5	Dengue
b_2	*Ae. albopictus*	0.5	Dengue
β_1	*Ae. aegypti*	0.1	Chouin-Carneiro et al. (2016)
β_2	*Ae. albopictus*	0.033	Chouin-Carneiro et al. (2016)

Extrinsic incubation periods

As there was no EIP estimates available for Zika, we had to revert to dengue again.[5] We used the dengue EIP fitting specific to *Ae. aegypti* of Liu-Helmersson et al. (2014) that is based on data of Watts et al. (1987). As dengue takes slightly longer in *Ae. albopictus* to develop, the

[5]There have been a couple of studies on ZIKV published in the meantime, indicating that EIPs for both *Ae. aegypti* and *Ae. albopictus* are in the range of 3 to 21 days (Boyer et al., 2018).

EIP function was adjusted by a scaling factor of 1.03 (Brady et al., 2014), see Figure A5.3.

As for Zika, there are no laboratory studies available that examine the incubation period of chikungunya at different temperatures. Tsetsarkin et al. (2007) suggested that the single point mutation in CHIKV increases its fitness for *Ae. albopictus* such that the EIP is shortened. At 28 °C, the EIP in *Ae. albopictus* can be as short as 2 days, but the average might be more around 6 days (Dubrulle et al., 2009). To fit this observation, we used the EIP function for dengue but lowered it by 3 days, see Table A5.9.

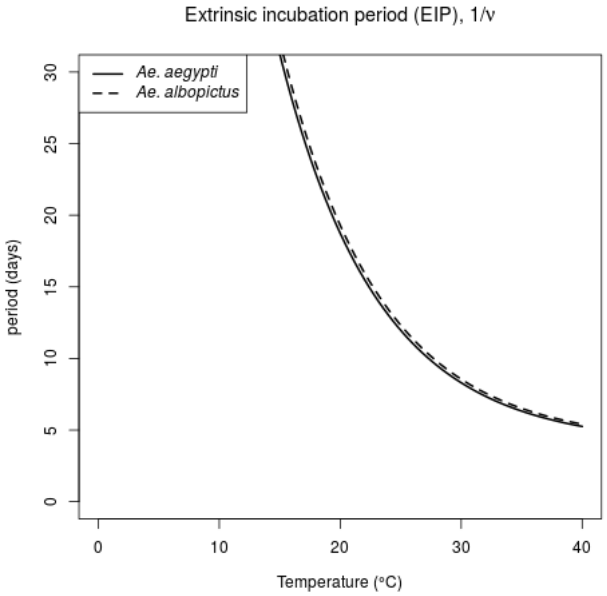

Figure A5.3: Extrinsic incubation periods EIP for the dengue virus in each *Aedes* vectors.

Table A5.9: Extrinsic incubation periods EIPs for *Aedes* vectors and viruses, depending on temperature T.

Dengue & Zika

Parameter	Vector	EIP
$1/\nu_1$	*Ae. aegypti*	$4 + exp(5.15 - 0.123\,T)$
$1/\nu_2$	*Ae. albopictus*	$1.03 \cdot (4 + exp(5.15 - 0.123\,T))$

Chikungunya

Parameter	Vector	EIP
$1/\nu_1$	*Ae. aegypti*	$4 + exp(5.15 - 0.123\,T)$
$1/\nu_2$	*Ae. albopictus*	$1 + exp(5.15 - 0.123\,T)$

Human recovery rate

The longer the human host stays infected, the higher the chance of mosquito bites and passing the disease on. For Zika, we used data from Musso et al. (2015) who found ZIKV undetectable

in blood and saliva after 7, resp. 8 days after symptoms onset and set the human recovery rate to 7 days. Recovery rates for chikungunya are similar, being in the range of 4 to 8 days (Carey et al., 1969; Parola et al., 2006). Only dengue seems to have slightly shorter symptomatic periods, ranging from 2 to 7 days (Gubler, 1998; WHO, 2009).

Table A5.10: Human recovery rate The inverse of the time period spent by humans in the symptomatic, infectious state.

Parameter	Virus	Recovery rate
r	Dengue	1/5
r	Chikungunya	1/7
r	Zika	1/7

A5.3 Monthly Zika Transmission Risk in 2015

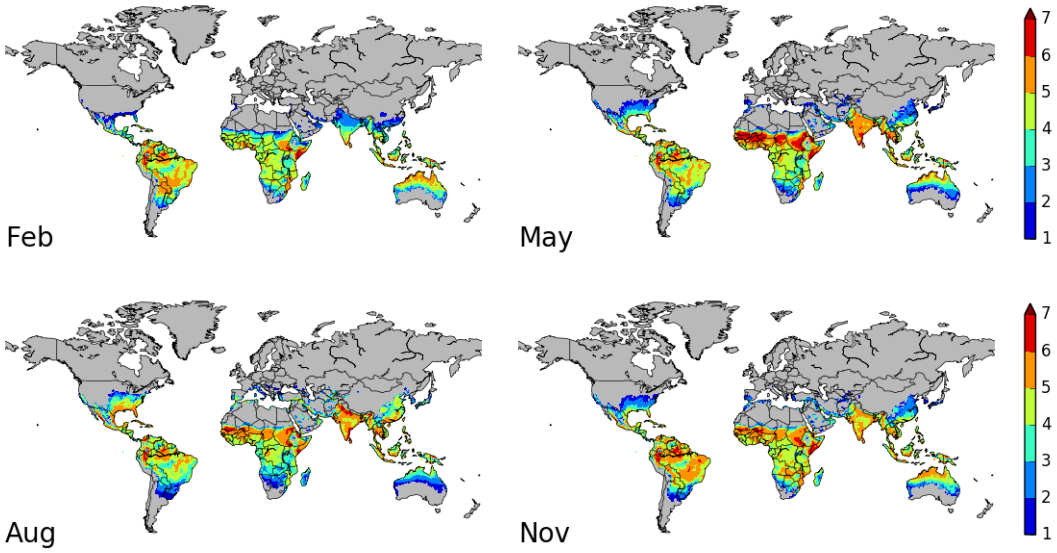

Figure A5.4: Monthly R_0 values for 2015. The seasons, shifting transmission hotspots north and south, are clearly visible.

A6.1 Development Times for Larval Instars

Tables A6.1, A6.3 and A6.3 show mean development times and survival probabilities for each instar stage (L1, L2, L3 and L4), the pupal stage (P), the total larval stage (L1 - P), and the total aquatic stage (L1 - A), for both *Ae. albopictus* and the *Ae. aegypti* strains.

Table A6.1: Mean development times and survival probabilities for *Ae. aegypti* aquatic stages.

	Development period [days]						
	L1	**L2**	**L3**	**L4**	**P**	**L1 - P**	**L1 - A**
12 °C	19.0	15.0	10.0	-	-	-	-
15 °C	6.3	3.2	5.7	14.4	8.1	28.4	35.7
18 °C	3.8	1.2	1.7	8.5	4.9	14.9	19.8
24 °C	1.0	1.1	1.2	4.0	2.6	7.1	9.8
	Survival probability [%]						
	L1	**L2**	**L3**	**L4**	**P**	**L1 - P**	**L1 - A**
12 °C	29	14	33	0	-	0	0
15 °C	98	97	96	73	69	67	46
18 °C	99	100	99	96	99	94	93
24 °C	99	100	100	98	99	97	96

Table A6.2: Mean development times and survival probabilities for tropical *Ae. albopictus* aquatic stages.

	Development period [days]						
	L1	**L2**	**L3**	**L4**	**P**	**L1 - P**	**L1 - A**
12 °C	25.6	21.3	-	-	-	-	-
15 °C	7.3	6.0	4.7	13.4	8.9	31.1	39.9
18 °C	4.5	1.4	2.3	7.9	5.5	15.7	21.1
24 °C	2.8	0.5*	1.0*	3.9	2.7	8.2	10.9
	Survival probability [%]						
	L1	**L2**	**L3**	**L4**	**P**	**L1 - P**	**L1 - A**
12 °C	12	64	0	-	-	0	0
15 °C	68	100	99	97	90	67	60
18 °C	88	100	100	99	100	88	88
24 °C	87	100	97	100	100	84	84

* When larvae developed from L1 to L3 within 24 hours, we recorded $^1/_2$ days for development in L2 etc.

A6.2 Data Comparison

The found development times, survival and blood-feeding behaviour can be compared with published data, see Figure A6.2 for *Ae. albopictus* and Figure A6.1 for *Ae. aegypti*. The daily mortality rates are estimated as shown in appendix A2.1.

Development times for *Ae. albopictus* are more on the upper range of what has been found for low temperatures, while they more on the lower range for *Ae. aegypti*. Daily survival rates are very similar to what has been found.

Table A6.3: Mean development periods for temperate *Ae. albopictus* aquatic stages in days.

Development period [days]							
	L1	**L2**	**L3**	**L4**	**P**	**L1 - P**	**L1 - A**
12 °C	43.0	-	-	-	-	-	-
15 °C	9.2	4.9	5.3	14.9	9.1	34.0	42.5
18 °* C	5.1	3.0	4.2	9.0	5.7	21.1	25.3
24 °C	2.7	1.4	1.8	3.9	2.6	9.7	12.4
Survival probability [%]							
	L1	**L2**	**L3**	**L4**	**P**	**L1 - P**	**L1 - A**
12 °C	2	0	-	-	-	0	0
15 °C	74	97	96	87	93	61	57
18 °C*	100	98	100	94	89	92	82
24 °C	99	100	99	96	86	94	81

∗ One replicate at 18 °C experienced a mortality of 96% in the L1 stage within a few days (possibly because the pan was contaminated). We excluded this replicate from analysis and calculated values with the 50 larvae of the other replicate.

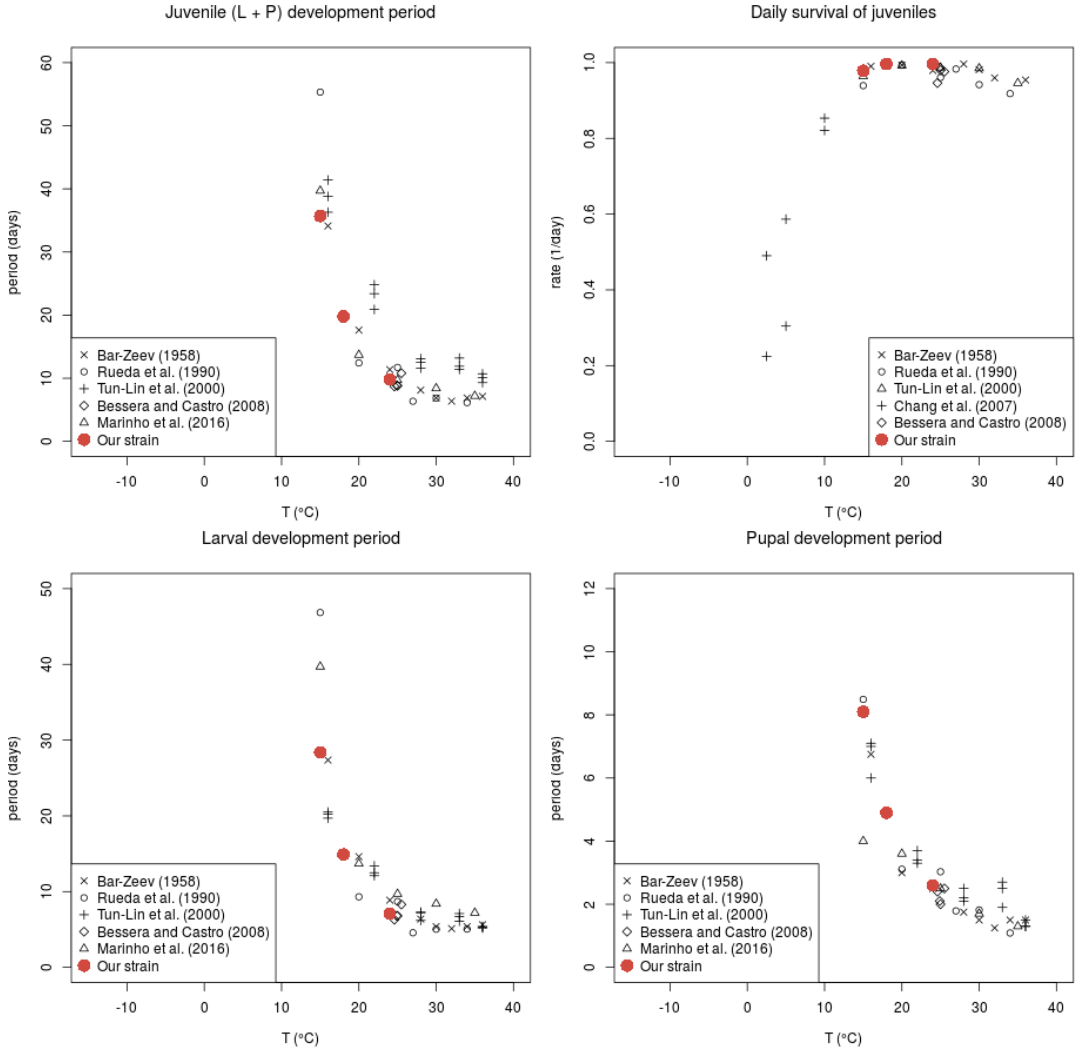

Figure A6.1: Development periods and survival rates of different *Ae. aegypti* stages.

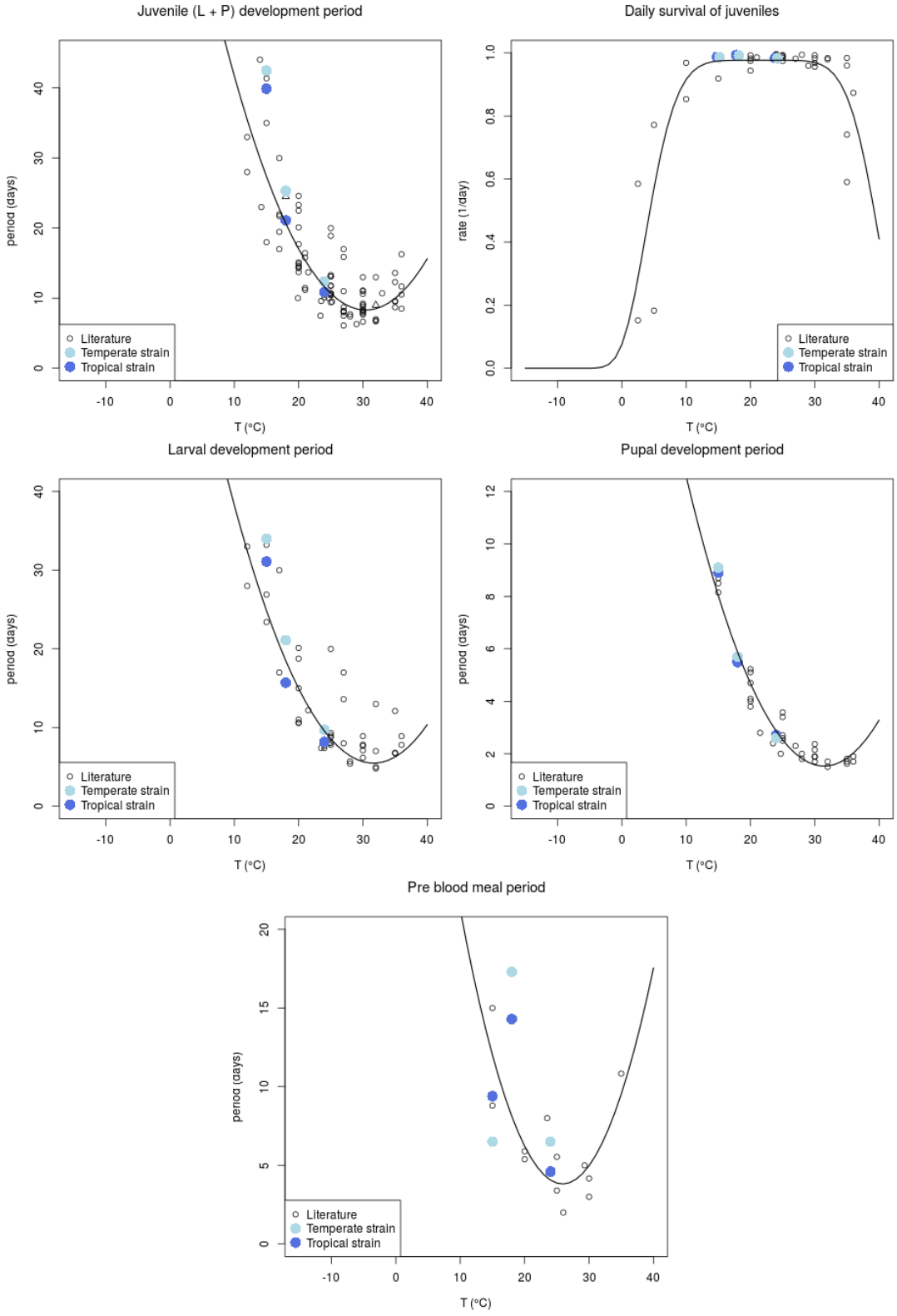

Figure A6.2: Development periods and survival rates of different *Ae. albopictus* stages. Data found for tropical and temperate larvae and pupae is well in the range of what has been published. The pre-blood meal period is varying, due to low numbers recorded. For full reference details, see Figures A1.1 and A1.2 in chapter 2. The black lines are the fitted curves used for the life cycle model in chapter 2.